Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections: Clinical Description of the First 50 Cases

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Objective: *The purpose of this study was to describe the clinical characteristics of a novel group of patients with obsessive-compulsive disorder (OCD) and tic disorders, designated as pediatric autoimmune neuropsychiatric disorders associated with streptococcal (group A β-hemolytic streptococcal [GABHS]) infections (PANDAS).* *Method:* *The authors conducted a systematic clinical evaluation of 50 children who met all of the following five working diagnostic criteria: presence of OCD and/or a tic disorder, prepubertal symptom onset, episodic course of symptom severity, association with GABHS infections, and association with neurological abnormalities.* *Results:* *The children's symptom onset was acute and dramatic, typically triggered by GABHS infections at a very early age (mean=6.3 years, SD=2.7, for tics; mean=7.4 years, SD=2.7, for OCD). The PANDAS clinical course was characterized by a relapsing-remitting symptom pattern with significant psychiatric comorbidity accompanying the exacerbations; emotional lability, separation anxiety, nighttime fears and bedtime rituals, cognitive deficits, oppositional behaviors, and motoric hyperactivity were particularly common. Symptom onset was triggered by GABHS infection for 22 (44%) of the children and by pharyngitis (no throat culture obtained) for 14 others (28%). Among the 50 children, there were 144 separate episodes of symptom exacerbation; 45 (31%) were associated with documented GABHS infection, 60 (42%) with symptoms of pharyngitis or upper respiratory infection (no throat culture obtained), and six (4%) with GABHS exposure.* *Conclusions:* *The working diagnostic criteria appear to accurately characterize a homogeneous patient group in which symptom exacerbations are triggered by GABHS infections. The identification of such a subgroup will allow for testing of models of pathogenesis, as well as the development of novel treatment and prevention strategies.*

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This is the first comprehensive report of a group of patients with childhood-onset obsessive-compulsive disorder (OCD) and tic disorders. The children have different primary diagnoses, including both OCD and tic disorders, but share in common a clinical course characterized by dramatic symptom exacerbations following group A β-hemolytic streptococcal (GABHS) infections. Sir William Osler was actually the first to notice such a relationship when he described "a certain perseverativeness of behavior" in patients with Sydenham's chorea, a variant of rheumatic fever (1). Aside from a few isolated reports (2–4), the importance of his prescient observations went unnoticed until the late 1980s, when we undertook a series of investigations directed at the hypothesis that basal ganglia dysfunction could cause a wide variety of neuropsychiatric symptoms depending upon the nature of both the environmental trigger and the host susceptibility (5). Support for this hypothesis had been provided by pathological reports of basal ganglia involvement in Sydenham's chorea (6) and neuropsychological and neuroimaging evidence of basal ganglia dysfunction in both Sydenham's chorea and OCD (7–11), as well as demonstrations of similar antineuronal antibodies in both disor-

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ders (5, 12–14). Further support was generated from longitudinal studies of children and adolescents with OCD and from systematic evaluation of children with Sydenham's chorea. Studies of Sydenham's chorea revealed that obsessive-compulsive symptoms were common during the illness (present in nearly three-quarters of children) and had their onset shortly before the chorea began, suggesting that the obsessive-compulsive symptoms were not "compensatory" for physical disability (because the children were not yet ill when they began to experience obsessions and compulsive rituals) (15, 16). On the basis of these observations, we postulated that children might exhibit only tics or OCD if the "dose" of a presumed etiologic agent was not sufficient to cause frank chorea (5).

Longitudinal follow-up of a group of children and adolescents with OCD revealed that a subgroup of the children had an episodic course characterized by dramatic and acute symptom exacerbations interspersed with periods of relative symptom quiescence (17–19). Of particular note, these exacerbations often followed infections with GABHS. The clinical course of a 10-year-old boy examined early in 1991 is illustrative.

Patient A presented to the child psychiatry clinic with a 2-week history of severe obsessive concerns about contamination from AIDS and other germs, cleaning and hoarding rituals, a nearly constant spitting tic, and choreiform movements (neurologically distinct from chorea). The symptoms had begun abruptly "overnight" and had progressed over a 48-hour period to the point where A was unable to attend school or participate in his usual extracurricular activities. His mother, a medical technologist, brought our attention to the fact that he had been diagnosed with GABHS pharyngitis less than 2 weeks before the onset of these symptoms. She had noted that her older son's tic disorder also had an episodic pattern, with exacerbations typically occurring a few days after he had been ill with a streptococcal pharyngitis; she suggested that "there had to be a connection between the two" events. At the time of initial presentation, A's antistreptococcal antibody titers were markedly elevated (threefold rise), and antineuronal antibody titers (12, 14) were positive. Over the next few weeks, A's OCD symptoms decreased in severity to a subclinical level (occasional contamination obsessions but no spitting, hoarding, or hand washing), and his antibody titers also fell. About 8 months later, after another GABHS infection, A had a dramatic symptom exacerbation, which was again associated with increased antibody titers, and then, slow resolution of his symptoms with a concomitant diminution of titers. Over the ensuing 2 years, each time A's symptoms increased and his medication dose required an upward adjustment, he had positive antistreptolysin O titers; during periods of remission, he was seronegative.

These clinical observations led to the proposal of a unique subgroup of patients with neuropsychiatric disorders that could be identified by the following criteria: 1) presence of OCD and/or a tic disorder, 2) prepubertal symptom onset, 3) episodic course of symptom severity, 4) association with GABHS infection, and 5) association with neurological abnormalities. The five criteria appeared to reliably identify a group of children who shared a common clinical course and were presumed to have a similar pathophysiology. The criteria reflect an underlying hypothesis that autoimmunity mediates the neuropsychiatric symptoms, and so the group was designated by the acronym PANDAS, for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

This report describes the first 50 children meeting the working diagnostic criteria for PANDAS and, in addition, discusses the clinical implications of such a diagnosis and proposes a model of pathogenesis.

METHOD

Establishing the Working Criteria for Diagnosis of PANDAS

Systematic clinical evaluation of children with Sydenham's chorea suggested that specific clinical characteristics might define a homogeneous subgroup of patients with OCD and tic disorders, including Tourette's disorder. Five working criteria were formulated (20) and have been modified slightly, as follows:

1. Presence of OCD and/or a tic disorder: The patient must meet lifetime diagnostic criteria (DSM-III-R or DSM-IV) for OCD or a tic disorder.
2. Pediatric onset: Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty (as is generally true for rheumatic fever [21]).
3. Episodic course of symptom severity: Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Often, the onset of a specific symptom exacerbation can be assigned to a particular day or week, at which time the symptoms seemed to "explode" in severity. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.
4. Association with GABHS infection: Symptom exacerbations must be temporally related to GABHS infection, i.e., associated with positive throat culture and/or elevated anti-GABHS antibody titers. Of note, the temporal relationship between the GABHS infection and the symptom exacerbation may vary over the course of the illness. In rheumatic fever, there is often a delay of 6–9 months between the last documented GABHS infection and the appearance of symptoms of Sydenham's chorea; however, recrudescences follow the GABHS infections at a much shorter interval, often with a time lag of only several days to a few weeks (22). It appears that the pattern is similar for PANDAS. It should be further noted that because fever and other stressors of illness are known to increase symptom severity, the exacerbations should not occur exclusively during the period of acute illness. Furthermore, as in Sydenham's chorea and rheumatic fever, some symptom recurrences may not be associated with documented GABHS infections (23), so the child's lifetime pattern should be considered when making the diagnosis.
5. Association with neurological abnormalities: During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common. Of note, children with primary OCD may have normal results on neurological examination, particularly during periods of remission. Further, the presence of frank chorea would suggest a diagnosis of Sydenham's chorea, rather than PANDAS. It is particularly important to make this distinction, since Sydenham's chorea is a known variant of rheumatic fever and requires prophylaxis against GABHS; PANDAS does not.

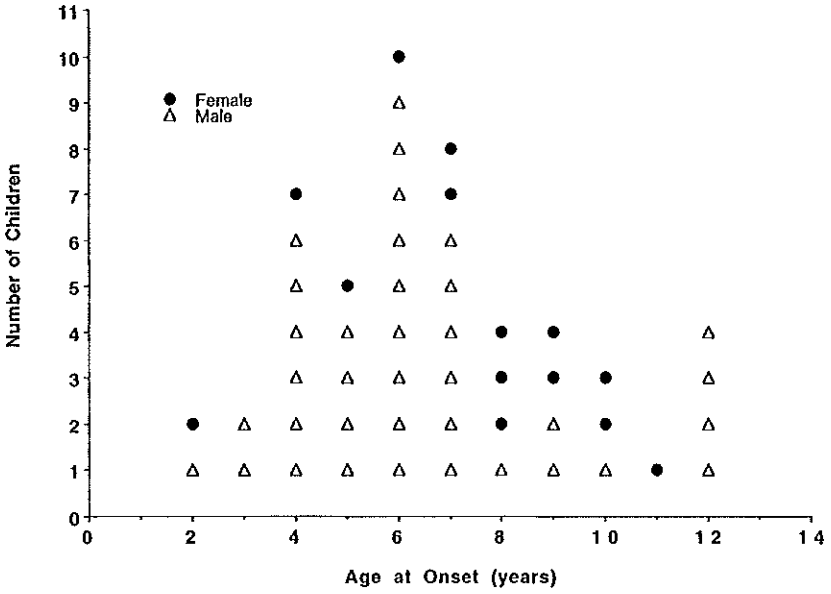
The diagnostic criteria were applied retrospectively to patients seen between 1991 and 1993 and prospectively to those seen thereafter. Each case was presented at a case conference, and consensus opinion was used to determine whether or not the child should be included in the PANDAS category. The assigned diagnoses were then independently confirmed by two of us (H.L.L. and S.E.S.) by strict application of the diagnostic criteria to case summaries; both authors were in complete agreement about the 50 PANDAS and 32 non-PANDAS cases reviewed.

TABLE 1. Demographic Characteristics of 50 Children With PANDAS[a]

Characteristic	Value	
	Mean	*SD*
Age at baseline evaluation (years)	9.3	2.6
Age at onset of obsessions/compulsions (years)	7.4	2.7
Age at onset of tics (years)	6.3	2.7
	N	*%*
DSM-III-R or DSM-IV diagnosis		
Subclinical OCD with tics or OCD and tics	32	64
Tics only	8	16
OCD only	10	20
OCD		
Meets DSM-IV criteria	28	56
Subclinical	14	28
None	8	16
Tics		
Tic disorder	40	80
None	10	20

[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The ratio of boys to girls was 2.6:1.

FIGURE 1. Age at Onset for Boys and Girls With PANDAS[a] (N=50)



[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

As a further test of the validity of the PANDAS working diagnostic criteria, 20 screening histories (10 PANDAS and 10 non-PANDAS cases) were selected by one of us (L.L.) and identifying information was removed. Five raters (B.K.D., M.G., H.L.L., S.P., and S.E.S.) independently applied the diagnostic criteria to the case summaries, and each rater correctly identified all 20 cases (kappa=1.0).

Subjects

Children with an acute onset or dramatic exacerbations of obsessive-compulsive symptoms and/or tics were sought through mailings to child psychiatrists, pediatricians, and pediatric neurologists, as well as through advertisements in the Tourette's Syndrome Association national newsletter. The advertisements did not include mention of infectious agents as a trigger. The local Tourette's Syndrome Association chapter and the national Obsessive Compulsive Foundation also served as sources of patient referrals. In addition, referrals were sought through presentations at national meetings and direct contact with physicians. As might be expected, referrals were initially limited (one or two patients per month) but increased gradually to the point where we currently conduct four to six telephone screenings per week.

At the time of this report, 270 telephone screenings had been conducted; of these, 109 subjects were invited to come to the National Institute of Mental Health (NIMH) for an in-person screening evaluation. The screening evaluation was conducted by at least two physicians (S.E.S., H.L.L., A.J.A., M.G., and/or S.P.) and consisted of a review of the child's medical records and a clinical interview with the child and his or her parents—this included a complete assessment of the history of the OCD and/or tic disorder and emphasized the chronology of the child's neuropsychiatric symptoms in relationship to environmental triggers.

Children were excluded from study participation if they had a history of Sydenham's chorea, rheumatic fever, or another autoimmune disorder or if examination revealed cardiac abnormalities consistent with prior rheumatic carditis (none of the children was excluded for heart disease.) They were also excluded if they failed to meet the working criteria for the diagnosis of PANDAS; of note, 27 children were excluded at the time of the in-person screening because the interview revealed that they did not have a clear association between streptococcal infections and symptom exacerbations; 32 children were excluded following baseline evaluation. Thus, 50 children met the working diagnostic criteria for PANDAS and are the subjects of this report.

Depending upon their symptom acuity, the children were enrolled in one of two protocols—a placebo-controlled study of penicillin prophylaxis or a randomized-entry controlled study of various immunomodulatory treatments (for acutely ill patients). Both studies had appropriate institutional review board review and approval. All subjects gave written assent, and their parents written consent, to participate in the research investigations.

Procedure

At baseline, subjects completed a battery of neuropsychological tests and a limited number of psychological tests to assess general intelligence level (5, 10). Parents provided historical information about their child (Diagnostic Interview for Children and Adolescents, revised, parent version) (24, 25), themselves (medical history and Schedule for Affective Disorders and Schizophrenia [26]), and their family members (semistructured family history; instrument available from Dr. Swedo upon request). The subjects underwent systematic medical and psychiatric assessment, including a structured psychiatric interview (Diagnostic Interview for Children and Adolescents, revised, child version) (24, 25) and standardized neurological examination (unpublished examination, available from Dr. Garvey upon request, and the Physical Assessment of Neurologic Subtle Signs examination [27]). Choreiform movements (small, jerky movements occurring irregularly and arrhythmically in different muscles) were assessed by using a modification of the guidelines outlined by Touwen (28). Proximal and distal movements were scored together. A score was assigned according to the amplitude and frequency of the movements over a 30-second period: 0=no movements observed; minimal=occasional small-amplitude movements of fingers; moderate=continuous, small-amplitude movements of fingers, wrists, and proximal areas (arms/shoulders); marked=continuous, moderate-amplitude movements of fingers, wrists, and proximal areas.

The child's neuropsychiatric symptom severity was rated at baseline by using a variety of semistructured scales, including the

TABLE 2. OCD Symptoms of 50 Children With PANDAS[a] and Primary OCD or Primary Tic Disorder

	Primary OCD (N=24)		Primary Tic Disorder (N=26)		Total (N=50)	
Symptom	N	%	N	%	N	%
Obsessions						
Contamination	16	67	9	35	25	50
Harm to self	9	38	2	8	11	22
Harm to others	10	42	7	27	17	34
Violent images	8	33	4	15	12	24
Sexual	9	38	1	4	10	20
Hoarding	8	33	4	15	12	24
Magical	8	33	4	15	12	24
Somatic	11	46	3	12	14	28
Religious	9	38	5	19	14	28
Other	11	46	10	38	21	42
Compulsions						
Washing, cleaning, spitting	15	63	6	23	21	42
Checking	12	50	7	27	19	38
Repeating	14	58	12	46	26	52
Counting	4	17	2	8	6	12
Ordering, arranging, table setting	12	50	8	31	20	40
Hoarding	6	25	3	12	9	18
Superstitious	2	8	1	4	3	6
Involves other persons	7	29	3	12	10	20
Other	17	71	11	42	28	56

[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Yale-Brown Obsessive Compulsive Scale (29, 30), Shapiro tic severity rating (31), Global Assessment Scale (32), and NIMH ratings of global, OCD, depression, and anxiety symptom severity (33, 34), as well as three scales designed specifically for use with these children: NIMH irritability, tic severity, and attention deficit hyperactivity disorder (ADHD) severity scales (instruments were modified from the NIMH OCD rating scale and are also available from Dr. Swedo upon request).

Baseline laboratory studies included CBC with WBC differential, erythrocyte sedimentation rate, standard tests of thyroid function, blood chemistries including osmolality and electrolytes, and an immunologic panel that included antinuclear antibody titer and quantitative immunoglobulin levels, among others. (These laboratory studies have not yet been systematically analyzed, and results are not presented in this article.) Each child also had a throat culture for GABHS, antistreptolysin O titers, and antistreptococcal DNAase B titers.

RESULTS

The demographic data for the 50 subjects are shown in table 1. Of particular note is the young age of this group and the early age at onset of both obsessive-compulsive symptoms and tics. The children were evenly divided between those with a primary diagnosis of OCD (N=24, 48%) and those with primary tic disorder (N=26, 52%); 43 (86%) of the children reported obsessive-compulsive symptoms, and 40 (80%) of the children were found to have motor tics. Boys outnumbered girls by a ratio of 2.6:1; below age 8 years, the ratio was 4.7:1. Figure 1 shows this gender distribution plotted against age at onset.

TABLE 3. Severity of Symptoms for Children With PANDAS[a] and Primary Tic Disorder or Primary OCD

	Score					
	Primary Tic Disorder (N=26)		Primary OCD (N=24)		Total (N=50)	
Rating Scale	Mean	SD	Mean	SD	Mean	SD
NIMH Obsessive-Compulsive Scale	4.0	2.5	8.2	3.1	5.9	3.5
Yale-Brown Obsessive Compulsive Scale sum						
Obsessions	8.5	2.8	12.0	5.3	10.5	4.7
Compulsions	5.6	4.9	11.7	6.0	9.1	6.3
Global Assessment Scale	71.0	13.2	56.6	13.6	64.7	15.1
Shapiro tic severity rating						
Motor tics, historical	11.1	4.7	10.1	5.0	10.8	4.7
Vocal tics, historical	8.7	6.1	8.6	5.6	8.7	5.9

[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Symptoms of OCD varied by primary diagnosis (table 2). Children with primary OCD reported more washing and checking behaviors than did children with a primary diagnosis of tic disorder (washing: χ^2=7.9, df=1, p=0.005; checking: χ^2=2.8, df=1, p=0.09).

The severity of the obsessive-compulsive symptoms was moderate, on average, as were motor and vocal tics (table 3).

Psychiatric comorbidity (table 4) was common for the children with PANDAS. ADHD, affective disorders, and anxiety disorders were most prevalent (40%, 42%, and 32%, respectively).

The symptoms of the comorbid diagnoses (particularly ADHD) were also reported to be exacerbated following streptococcal infections, although this was not assessed systematically. In addition, a number of behavioral symptoms were noted to have had their onset concomitant with the onset of the OCD/tics and to have a relapse-remission pattern similar to that of the tics and obsessive-compulsive symptoms. These symptoms are listed in table 5. Most notable among them were emotional lability, separation anxiety, motoric hyperactivity and "fidgetiness," age-inappropriate behavior, and nighttime difficulties, including severe nightmares and new bedtime fears/rituals (e.g., needing to have a nightlight, sleeping outside the parents' bedroom). The symptoms were quite distressing to the children and were clearly distinguishable from the child's premorbid state. These comorbid symptoms always started abruptly, at the same time as the obsessive-compulsive symptoms and tics began or worsened, and were also associated with an increase in antistreptococcal antibody titers.

Association With Neurological Abnormalities

As previously described, 40 children (80%) had a tic disorder. No child had overt chorea, by history or examination. Formal testing for choreiform movements

TABLE 4. Comorbid Diagnoses of 50 Children With PANDAS[a]

Diagnosis	Patients N	Patients %
ADHD	20	40
Oppositional defiant disorder	20	40
Conduct disorder	2	4
Major depression	18	36
Dysthymia	6	12
Mania	0	0
Separation anxiety	10	20
Avoidant disorder	4	8
Overanxious disorder	14	28
Specific phobia	8	16
Eating disorder	1	2
Enuresis	6	12
Encopresis	5	10
Somatization disorder	0	0
Psychoses	0	0

[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

TABLE 5. Symptoms Associated With Exacerbations of PANDAS[a] in 50 Children

Symptom	Patients N	Patients %
Emotional lability	33	66
Change in school performance	30	60
Personality change	27	54
Bedtime fears/rituals	25	50
Fidgetiness	25	50
Separation anxiety	23	46
Irritability	20	40
Tactile/sensory defensiveness	20	40
Impulsivity/distractibility	19	38
Deterioration in handwriting	18	36
Oppositional/defiant	16	32
Deterioration in math skills	13	26
Nightmares	9	18

[a]Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

was performed with 26 of the 50 children. Only one child had no choreiform movements noted on baseline examination (although she subsequently demonstrated these movements). Marked choreiform movements were observed in 13 children (50%); five (19%) had moderate choreiform movements, and seven (27%) had minimal choreiform movements. Of note, and contrary to expectations that the movements would decrease with increasing age, a similar number of children above 10 years of age (N=4 of 7, 57%) and under the age of 10 (N=9 of 19, 47%) had marked choreiform movements (p=0.66, Fisher's exact test). Both the choreiform movements and the tics waxed and waned in severity over time, with exacerbations temporally linked to streptococcal infections in a manner similar to the obsessive-compulsive symptoms.

Association Between Symptom Exacerbations and Streptococcal Infections

Evidence of a temporal relationship between streptococcal infections and symptom exacerbations was obtained from parent history, by comparison of the child's pediatric (medical) records to his or her psychiatric records, and by prospective study. Symptom onset was associated with GABHS infection in 21 children (42%), with GABHS exposure in one child (2%), and with symptoms of pharyngitis (no throat culture obtained) in 14 subjects (28%). Each child also had at least one symptom exacerbation that was preceded (within the prior 6 weeks) by a documented GABHS infection. Among the 50 children, there were a total of 144 exacerbations in which the relationship to GABHS infection was known. Thirty-three (23%) of these were not associated with any sign of GABHS infection within the preceding month. However, the majority had at least some evidence of GABHS triggers: 45 (31%) exacerbations were associated with a positive throat culture or episode of scarlet fever (which is distinguished by a maculopapular rash pathognomonic for GABHS), six (4%) had a history of recent upper respiratory infection symptoms plus known GABHS exposure (sibling or close friend), and 60 (42%) had a sore throat or upper respiratory infection symptoms with fever, but no culture or titers were obtained. The last two categories represent possible GABHS infections, but it is not possible to make such a diagnosis in the absence of a positive throat culture or rising antistreptococcal antibody titers.

DISCUSSION

The 50 children with PANDAS described in this report share many clinical features in common with other groups of childhood-onset OCD and tic disorders. The obsessive-compulsive symptoms and patterns of motor and vocal tics are similar to those previously described, as is the frequency of comorbid depression and anxiety disorders (17–19, 31, 35–37). Boys outnumber girls, as has been previously reported for both tic disorders and early-childhood onset OCD. Indeed, the PANDAS patients appear to be remarkably similar to those with prepubertal symptom onset who were previously described as part of an unselected group of subjects with childhood-onset OCD (17).

The children with PANDAS had several unique clinical characteristics, as defined by the working diagnostic criteria and confirmed by observed symptom exacerbations.

1. Very-young-age-at-onset PANDAS is defined as a prepubertal disorder so that it is not surprising that the children had an early age at onset (6.3 years for tics and 7.4 years for obsessive-compulsive symptoms). However, the average age at onset of symptoms for this group was nearly 3 years younger than that for previous groups of childhood-onset OCD and tic disorders (17, 37).

2. Symptom exacerbations were sudden and dramatic and were associated with GABHS infections. Positive throat culture was the most frequent means of demon-

strating an association. Because of this, and because untreated GABHS infections can precipitate rheumatic fever, it was of concern to note how often sore throats with fever went uncultured. Because rheumatic fever continues as a risk of untreated GABHS infection, all parents should be encouraged to seek medical care whenever their school-age child has symptoms of GABHS pharyngitis, such as sore throat with fever, scarlatiniform rash, or a symptom triad of headache, stomachache, and fever (even without a sore throat).

Two clinical notes should be made. First, not all symptom exacerbations were preceded by GABHS infections; viral infections or other illnesses could also trigger symptom exacerbations. This is in keeping with the known models of immune responsivity—primary responses are specific (e.g., directed against a particular epitope on the GABHS), while secondary responses are more generalized. Thus, the lack of evidence for a preceding strep infection in a particular episode does not preclude the diagnosis of PANDAS. (Note, however, that the diagnosis cannot be made without establishing a clear association between GABHS infection and symptom exacerbation, preferably on at least two occasions.) Second, positive antistreptococcal titers obtained at the time of a single symptom exacerbation are not sufficient to prove that a child has PANDAS. Because antistreptococcal antibody titers may remain elevated for several months, longitudinal study is necessary to demonstrate that not only is seropositivity associated with symptom exacerbations, but also that seronegativity (or falling titers) is associated with symptom remission. Longitudinal study of a small number of children with PANDAS suggests that exacerbations are associated with a rapid, dramatic (twofold or higher) increase in antistreptococcal titers, while symptom remission and titer decreases occur more slowly. Data are currently being collected to further define this relationship.

3. Frequent association with motoric hyperactivity, impulsivity, and distractibility. The symptoms met criteria for ADHD, except that the onset frequently occurred after age 6 years. The children with PANDAS exhibited a peculiar "squirminess" in which the children tried very hard to sit still but constantly wriggled and fidgeted in their chairs. This was not chorea but was quite reminiscent of early descriptions of St. Vitus's dance.

4. Comorbid symptoms (emotional lability, separation anxiety, age-inappropriate behavior, and nighttime difficulties) were also episodic and temporally related to GABHS infections. The symptoms were present so frequently that it is tempting to speculate that they are also manifestations of the PANDAS phenomenon, particularly since the rates in this group of children are so much higher than expected in the community (38, 39). Perhaps the syndrome of PANDAS should be expanded to include primary diagnoses of late-onset ADHD and separation anxiety disorders, as well as OCD and tic disorders. It is possible that some or all of these may be manifestations of the pathophysiology leading to PANDAS. Further study will permit definition of the relationship between autoimmunity triggered by GABHS infection and other childhood neuropsychiatric disorders.

There are several limitations to this investigation that are worthy of note. First, many of our patients were referred through the local Tourette's Syndrome Association, which may have caused an overrepresentation of tic disorders among the study group. Epidemiologic studies and application of the PANDAS diagnostic criteria to unselected clinic populations will help ascertain whether or not tics are as common as reported here (80% of subjects). Second, the association of GABHS infection with symptom exacerbations was assigned retrospectively for the majority of episodes. Ideally, this relationship would be established by prospective analysis. For example, we established a 6-week cutoff for preceding GABHS infections. This may have excluded the triggering GABHS infection, since data from rheumatic fever studies demonstrate that the GABHS infection can precede symptom onset by several months (22, 23), although the lag between subsequent infections and symptom exacerbations is much shorter—often only a few days to a week apart. This temporal change is consistent with known models of immunity in which the primary response is slow and the secondary response is rapid (40).

The present data cannot be used to answer the question of how many children with neuropsychiatric disorders have PANDAS, nor can it inform us about the natural history of the disorder. What happens to these children? Do they comprise the one in seven individuals whose OCD and tic disorders spontaneously remit (41) because they outgrow their symptoms after they pass through the age of vulnerability? Or perhaps they are the unfortunate ones who have chronic, treatment-resistant OCD (42, 43) because repeated GABHS infections have caused irreversible damage to the basal ganglia. Answers to these questions will be obtained only by careful, systematic evaluation of this and other groups of patients with PANDAS.

We have previously speculated that obsessive-compulsive symptoms might be etiologically similar to Sydenham's chorea and rheumatic fever (5, 13). On the basis of what is known about the pathogenesis of rheumatic fever and our observations of this cohort of 50 children with PANDAS, we have developed the following model of pathogenesis of PANDAS: Pathogen + Susceptible Host → Immune Response → Sydenham's chorea or PANDAS (neuropsychiatric symptoms).

Application of the model permits the recognition of PANDAS as a distinct clinical syndrome. It also allows for the characterization of particular strains of GABHS that are prone to the induction of PANDAS in the susceptible host; the definition of factors that confer susceptibility for the development of PANDAS in an individual; the description of the immune response associated with the development of the clinical symptoms; and the identification of the structures and functions involved in the expression of the clinical symp-

toms. Each of the delineated points can be the focus of diagnostic testing and therapeutic intervention. The susceptible host might be rendered less susceptible by prevention of GABHS infections (antibiotic prophylaxis) or by immunization against GABHS infections. Infection of the host by pathogenic GABHS might be prevented by colonization of the host with nonpathogenic strains of the bacterium or by targeted anti-GABHS antimicrobials. The immune response might be influenced by the administration of adjuvants, cytokines, or immunomodulatory agents. End-organ pathology might be prevented by treatments aimed at removing pathogenic autoantibodies or stimulating the function of specific neural circuits or structures. Each of these arenas holds tremendous promise for future therapeutic interventions.

The possibility that pathogens other than GABHS can induce neuropsychiatric symptoms is suggested by the presence of non-GABHS-related exacerbations in the children with PANDAS, as has been reported for Sydenham's chorea (23). It is postulated that GABHS needs to be the initial autoimmunity-inciting event but that subsequent symptom exacerbations can be triggered by viruses, other bacteria, or noninfectious immunologic responses.

In the model of pathogenesis, host factors are also of critical importance. Male gender appears to be a risk factor, as three-quarters of the PANDAS subjects are male, but the mechanism of this increased vulnerability is unknown. The age of the host also may determine susceptibility; it is known that rheumatic fever is quite rare after puberty. It appears that the developmental changes of adolescence may decrease the vulnerability to the cross-reactive autoimmunity. It is also possible that the postpubertal decrease in incidence (44) is related to the fact that the rate of GABHS infections falls dramatically around the age of 12, presumably because the child has developed antibodies against the conserved portion of the M-protein (i.e., the child is able to make antibodies that recognize all strains of GABHS) (V. Fischetti, personal communication, 1994).

Genetic control of the immune response may contribute to differential vulnerability to PANDAS. Murine genetic models suggest that the response to infectious pathogens is strain specific. Different strains have responses that differ qualitatively and quantitatively and lead to very different clinical outcomes. For example, the immune response of BALB/c mice to infection with *M. leprae* or *S. mansoni* is extreme and leads to the death of the animal, whereas similar inocula in C57/BL6 mice cause self-limited infections (45, 46).

Familial factors may also play a role in the pathogenesis of PANDAS. "Rheumatogenic families," in which the incidence of rheumatic fever far exceeds that of the general population, were described first by Cheadle in 1889 (21). Preliminary studies of the mode of inheritance of this vulnerability suggest that the trait is autosomal recessive (47, 48) and that it may be related to a surface characteristic of peripheral blood mononuclear cells. Individuals who are susceptible to rheumatic fever have a high frequency of binding of a monoclonal antibody designated D8/17 (48). We have previously reported that patients with PANDAS have rates of D8/17 positivity similar to those seen in patients with rheumatic fever (and Sydenham's chorea, a rheumatic fever variant), and markedly different from rates found in healthy control subjects (49). The presence of a biological marker of susceptibility to rheumatic fever and PANDAS provides for the development of prophylactic strategies aimed at preventing the sequelae of GABHS disease in susceptible individuals by either altering host susceptibility or preventing GABHS infection.

CONCLUSIONS

The working diagnostic criteria appear to define a meaningful subgroup of patients with childhood-onset OCD and tic disorders; with further study, other neuropsychiatric symptoms may also be found to be appropriately included in the PANDAS spectrum. The identification of a subgroup of patients with PANDAS may be important from several aspects. First, children who develop OCD, tics, motoric hyperactivity, and other neuropsychiatric symptoms as sequelae of streptococcal infections (i.e., those with PANDAS) may share a common pathogenetic process that is distinct from other (non-PANDAS) cases of such disorders. This homogeneity may be related to genetic vulnerability or other definable biological factors. Second, if children with PANDAS share a common pathogenesis, therapies can be developed that are directed at correcting the underlying pathological process, rather than at mere symptom palliation alone. Third, hypothesis-driven research directed at defining the susceptible host, the specific triggers, the host-pathogen interaction, and the end-organ targeting of the pathogenetic process may shed light not only on PANDAS, but also on non-PANDAS neuropsychiatric symptoms. Our ongoing work in the phenomenology and pathogenesis of PANDAS is designed to address each of these issues.

REFERENCES

1. Osler W: On Chorea and Choreiform Affections. Philadelphia, HK Lewis, 1894, pp 33–35
2. Chapman AH, Pilkey L, Gibbons MJ: A psychosomatic study of eight children with Sydenham's chorea. Pediatrics 1958; 21:582–595
3. Freeman JM, Aron AM, Collard JE, MacKay MC: The emotional correlates of Sydenham's chorea. Pediatrics 1965; 35:42–49
4. Grimshaw L: Obsessional disorder and neurological illness. J Neurol Neurosurg Psychiatry 1964; 27:229–231
5. Swedo SE: Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. JAMA 1994; 272:1788–1791
6. Thiebaut F: Sydenham's chorea, in Handbook of Clinical Neurology, vol 8. Edited by Vinken P, Bruyn G. Amsterdam, North Holland, 1968, pp 409–436
7. Rapoport JL: The neurobiology of obsessive-compulsive disorder. JAMA 1989; 260:2888–2890
8. Goldman S, Amron D, Szliwowski HB, Detemmerman D, Gold-

man S, Bidaut LM, Stanus E, Luxen A: Reversible striatal hypermetabolism in a case of Sydenham's chorea. Mov Disord 1993; 8:355–358
9. Giedd JN, Rapoport JL, Kruesi MJ, Parker C, Schapiro MB, Allen AJ, Leonard HL, Kaysen D, Dickstein DP, Marsh WL, Kozuch PL, Vaituzis AC, Hamburger SD, Swedo SE: Sydenham's chorea: magnetic resonance imaging of the basal ganglia. Neurology 1995; 45:2199–2202
10. Casey BJ, Vauss YC, Chused A, Swedo SE: Cognitive functioning in Sydenham's chorea, parts I and II: attentional processes and executive functioning. Developmental Neuropsychology 1994; 10:75–96
11. Insel TR: Toward a neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry 1992; 49:739–744
12. Husby G, Van de Rijn I, Zabriskie JB, Abdin AH, Williams RC: Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. J Exp Med 1976; 144:1094–1110
13. Swedo SE, Leonard HL, Kiessling LS: Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics 1994; 93:323–326
14. Kiessling LS, Marcotte AC, Culpepper L: Antineuronal antibodies in movement disorders. Pediatrics 1993; 92:39–43
15. Swedo SE, Rapoport JL, Cheslow DL, Leonard HL, Ayoub EM, Hosier DM, Wald ER: High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. Am J Psychiatry 1989; 146:246–249
16. Swedo SE, Leonard HL, Schapiro MB, Casey BJ, Mannheim GB, Lenane MC, Rettew DC: Sydenham's chorea: physical and psychological symptoms of St Vitus dance. Pediatrics 1993; 91:706–713
17. Swedo SE, Rapoport JL, Leonard HL, Lenane MC, Cheslow D: Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 1989; 46:335–341
18. Leonard HL, Lenane MC, Swedo SE, Rettew DC, Gershon ES, Rapoport JL: Tics and Tourette's syndrome: a 2- to 7-year follow-up of 54 obsessive-compulsive children. Am J Psychiatry 1992; 149:1244–1251
19. Rettew DC, Swedo SE, Leonard HL, Lenane MC, Rapoport JL: Obsessions and compulsions across time in 79 children and adolescents with obsessive compulsive disorder. J Am Acad Child Adolesc Psychiatry 1992; 31:1050–1056
20. Allen AJ, Leonard HL, Swedo SE: Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1995; 34:307–311
21. Cheadle WB: The various manifestations of the rheumatic state as exemplified in children and early life. Lancet 1889; 1:821–827
22. Ayoub EM, Wannamaker LW: Streptococcal antibody titers in Sydenham's chorea. Pediatrics 1966; 38:946–956
23. Berrios X, Quesney F, Morales A, Blazquez J, Bisno AL: Are all recurrences of "pure" Sydenham chorea true recurrences of acute rheumatic fever? Pediatrics 1985; 10:867–872
24. Welner Z, Reich W, Herjanic B, Jung K, Amado H: Reliability, validity, and child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry 1987; 26:649–653
25. Reich W, Cottler L, McCallum K, Corwin D, VanEerdewegh M: Computerized interviews as a method of assessing psychopathology in children. Compr Psychiatry 1995; 36:40–45
26. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia (SADS), 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1982
27. Denckla MB: Revised neurological examination for subtle signs. Psychopharmacol Bull 1985; 21:773–793
28. Touwen BCL: Examination of the Child With Minor Neurological Dysfunction. Clinics in Developmental Medicine, vol 71. London, Heinemann, 1979, p 53
29. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS: The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 1989; 46:1012–1016
30. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS: The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 1989; 46:1006–1011
31. Shapiro AK, Shapiro ES, Young JG, Feinberg TE: Measurements in tic disorders, in Gilles de la Tourette Syndrome, 2nd ed. New York, Raven Press, 1988, pp 451–480
32. Endicott J, Spitzer RL, Fleiss JL, Cohen J: The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33:766–771
33. Murphy DL, Pickar D, Alterman IS: Methods for the quantitative assessment of depressive and manic behavior, in The Behavior of Psychiatric Patients. Edited by Burdock EL, Sudilovsky A, Gershon S. New York, Marcel Dekker, 1982, pp 355–392
34. Insel TR, Murphy DL, Cohen RM, Alterman I, Kilts C, Linnoila M: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 1983; 40:605–612
35. Pitman RK, Green RC, Jenike MA, Mesulam MM: Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. Am J Psychiatry 1987; 144:1166–1171
36. Holzer JC, Goodman WK, McDougle CJ, Baer L, Boyarsky BK, Leckman JF, Price LH: Obsessive-compulsive disorder with and without a chronic tic disorder: a comparison of symptoms in 70 patients. Br J Psychiatry 1994; 164:469–473
37. Thomsen PH, Mikkelsen HU: Course of obsessive compulsive disorder in children and adolescents: a prospective follow-up study of 23 Danish cases. J Am Acad Child Adolesc Psychiatry 1995; 34:1432–1440
38. Brandenburg NA, Friedman RM, Silver SE: The epidemiology of childhood psychiatric disorders: prevalence findings from recent studies. J Am Acad Child Adolesc Psychiatry 1990; 29:76–83
39. Costello EJ: Developments in child psychiatric epidemiology. J Am Acad Child Adolesc Psychiatry 1989; 28:836–841
40. Roitt IM, Brostoff J, Male DK: Essential Immunology, 4th ed. Baltimore, Mosby, 1996, p 31
41. Karno M, Golding JM, Sorenson SB, Burnam MA: The epidemiology of obsessive-compulsive disorder in five US communities. Arch Gen Psychiatry 1988; 45:1094–1099
42. Ravizza L, Barzega G, Bellino S, Bogetto F, Maina G: Predictors of drug treatment response in obsessive-compulsive disorder. J Clin Psychiatry 1995; 56:368–373
43. Ackerman DL, Greenland S, Bystritsky A, Morgenstern J, Katz RJ: Predictors of treatment response in obsessive-compulsive disorder: multivariate analysis from a multicenter trial of clomipramine. J Clin Psychopharmacol 1994; 14:247–254
44. Huovinen P, Lahtonen R, Ziegler T, Meurman O, Hakkarainen K, Miettinen A, Arstila D, Eskola J, Saikku P: Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. Ann Intern Med 1989; 110:612–616
45. Sher A, Gazzinelli RT, Oswald IP, Clerici M, Kullberg M, Pearce EJ, Berzofsky JA, Mosmann TR: Role of T-cell derived cytokines in the down regulation of immune responses in parasitic and retroviral injection. Immunol Rev 1992; 127:183–204
46. Castro AG, Minoprio P, Appleberg R: The relative impact of bacterial virulence and host genetic background on cytokine expression during Mycobacterium avium infection of mice. Immunology 1995; 85:556–561
47. Wilson MG, Schweitzer MD, Lubschez R: The familial epidemiology of rheumatic fever: genetic and epidemiologic studies. J Pediatr 1943; 22:468–492
48. Gibofsky A, Khanna A, Suh E, Zabriskie JB: The genetics of rheumatic fever: relationship to streptococcal infection and autoimmune diseases. J Rheumatol Suppl 1991; 30:1–5
49. Swedo SE, Leonard HL, Mittleman BB, Allen AJ, Rapoport JL, Dow SP, Kanter ME, Chapman F, Zabriskie J: Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. Am J Psychiatry 1997; 154:110–112

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From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

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Abstract

Despite continued debates about the role of Group A streptococcal infections in the etiopathogenesis of PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections), experts on both sides of the controversy agree that a subgroup of children with obsessive-compulsive disorder (OCD) have an unusually abrupt onset of symptoms, accompanied by a variety of comparably severe and acute neuropsychiatric symptoms. The acuity of symptom onset is the hallmark feature of their clinical presentation and the basis for the name proposed for an expanded clinical entity: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Modifying the PANDAS criteria to eliminate etiologic factors and to clarify the initial clinical presentation produced three potential diagnostic criteria for PANS. These three criteria are discussed in detail. The article also proposes strategies for applying the PANS criteria in clinical settings and evaluating their validity and reliability through prospective research investigations.

Introduction

When the initial description of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) was published in 1998, it was a compilation of more than a decade of research by clinical investigators in the intramural research program of the National Institute of Mental Health (NIMH) [1]. Establishing a connection between childhood-onset obsessive compulsive disorder (OCD) and preceding infections with Group A streptococcal (GAS) infections was the result of two parallel lines of research - longitudinal studies of OCD and a series of investigations of Sydenham chorea (SC) [2-4]. Prospective evaluations of children with OCD revealed that a subgroup had an atypical symptom course, characterized by an unusually abrupt onset (from no symptoms to maximum intensity within 24-48 hours), a relapsing-remitting symptom course, and significant neuropsychiatric comorbidity, including separation anxiety, ADHD-like symptoms and motor tics [1,2]. Often, the OCD symptoms were preceded by a bacterial or viral infection, such as influenza, varicella and Group A streptococcal (GAS) pharyngitis. The first case series suggested the name, "Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITANDS) "to reflect the variety of infectious organisms that had been observed [5]. Cases with onset of OCD symptoms following a GAS infection were of greatest interest to the NIMH investigators because of their concomitant research findings in SC which demonstrated that obsessions and compulsions were present in 60 – 75% of the affected children [3,6,7]. The children with SC reported that the obsessive-compulsive symptoms began 2 – 4 weeks prior to onset of the adventitious movements, leading the investigators to hypothesize that the neuropsychiatric symptoms might represent a *forme fruste* of SC and be manifest by children with a history of (untreated) GAS infections, even in the absence of chorea [6,7]. Dozens of post-GAS cases were subsequently identified and their unique clinical characteristics served as the basis for the diagnostic criteria for the PANDAS subgroup [1] (See Table 1).

Subsequent research at a number of institutions revealed that not only are there clinical similarities between SC and PANDAS [8-11] but the two disorders also have similar profiles of cross-reactive antineuronal antibodies [12-15], responses to immunomodulatory therapies [16-17] and vulnerability to non-GAS recurrences [18-20]. Despite these commonalities, it is important to note that PANDAS is not equivalent to a "mild case of SC", as the presence of chorea, rheumatic carditis or any of the other major manifestations of rheumatic fever (RF) is an exclusionary criterion for PANDAS [1,21]. By ruling out RF and SC before considering a diagnosis of PANDAS, decisions about antibiotic prophylaxis can be made appropriately. Clinical practice guidelines from the American Heart Association require antibiotics prophylaxis for all cases of RF, including those presenting only with chorea [22]. In contrast, antibiotics prophylaxis is not generally recommended for children in the PANDAS subgroup. Although two separate clinical trials in PANDAS demonstrated that

All five diagnostic criteria must be met:

1) Presence of obsessive-compulsive disorder (OCD) or a tic disorder

2) Prepubertal symptom onset

3) Acute symptom onset and episodic (relapsing-remitting) course

4) Temporal association between Group A streptococcal infection and symptom onset/exacerbations

5) Associated with neurological abnormalities, (particularly motoric hyperactivity and choreiform movements)

Table 1: PANDAS Diagnostic Criteria.

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prevention of GAS infections was associated with decreased numbers of neuropsychiatric symptom exacerbations and overall improvements in symptom severity, the results were not considered generalizable to the larger population of PANDAS patients because both studies were limited by methodological constraints, including small sample sizes [23-24].

The NIMH investigators' decision to limit their investigations to the PANDAS subgroup, rather than the broader category of PITANDS, was a research strategy designed to take advantage of knowledge gained from studies of SC and rheumatic fever [7-8]. As other groups also directed their research efforts towards the role of GAS infections in the etiology of OCD and other neuropsychiatric symptoms, attention was diverted from the larger class of post-infectious neuropsychiatric disorders. A few cases of OCD and tic disorders occurring after mycoplasma infections or in association with chronic Lyme disease were reported [25-27], but these anecdotal reports have not been replicated and extended through systematic investigations, so it remains unknown whether those microorganisms play an etiologic role in acute-onset OCD and tic disorders. Further research is warranted to determine which microorganisms produce sequelae that include acute-onset neuropsychiatric symptoms and to investigate the variety of etiologies and pathogenic mechanisms.

The requirement that PANDAS patients demonstrate "temporal association of neuropsychiatric symptom onset with preceding GAS infection" created difficulties for clinicians, who often were confronted with patients who met all criteria for the PANDAS subgroup, except for evidence of a preceding GAS infection [28]. Unfortunately, establishing an etiologic role for GAS in the onset of PANDAS is often as difficult as it is for SC, where the chorea may lag behind the inciting GAS infection by six months or longer [6,29]. By then, the GAS infection has been cleared from the throat (so cultures are negative) and the rise in antibody titers has already occurred, so it is no longer possible to establish a causal relationship between GAS and the neuropsychiatric symptoms. Spuriously positive associations are similarly problematic, as positive cultures and elevated antibody titers may be completely unrelated to the neuropsychiatric symptoms, since GAS infections are such a common occurrence among school-age children [30]. Additional impediments to establishing GAS as the etiologic agent in PANDAS include the need for an appropriately performed throat culture to differentiate GAS pharyngitis from other pathogens; the lack of sensitivity of rapid strep tests and throat cultures (5-15% false negatives), the presence of a carrier state among 1 in 20 children, and the need for serial measurements of anti-streptococcal titers at specified intervals in order to document an immune response to an acute infection [31-32]. Prospective, longitudinal investigations would appear to be the solution to this problem, as they are designed to detect GAS infections which precede exacerbations of neuropsychiatric symptoms, but those studies also may fail to establish an etiologic relationship, since the cross-reactive antibodies may be nonspecifically released during the early, innate immune response [33]. A generalization of the immune response might provide a partial explanation for the results of two recent prospective studies of children with tic disorders, which found increased numbers of neuropsychiatric exacerbations following a variety of immune stimulants, including viral infections and psychosocial stressors, as well as after GAS infections [19-20,34].

An additional problem encountered in the prospective longitudinal studies was the lack of clear separation between PANDAS cases and non-PANDAS cases [19-20]. Difficulties distinguishing the "acute, dramatic onset" of tics in the PANDAS subgroup from the typically "acute" onset of tics in non-PANDAS tic disorders were predicted by the fact that both are described as having an "off-on" onset [35]. Indeed, studies that did not clearly establish acuity of onset for their PANDAS cases found few differences between the cases and non-PANDAS controls [19-20,34]. The overlap not only limited the results of the clinical studies, but also impacted laboratory studies dependent upon clear separation of cases and controls [36]. Not surprisingly, such studies produced negative data, which was interpreted as refuting the PANDAS hypothesis. In contrast, studies that adhered closely to the PANDAS diagnostic criteria produced positive data and were seen as supporting a role for GAS in the etiology of neuropsychiatric symptoms (reviewed by Murphy et al. [37]). Adding to the confusion of the conflicting data reports were editorial debates about the validity of the PANDAS subgroup and the utility of its hypothesized etiology [38-41]. The resulting "PANDAS controversy" adversely affected researchers, clinicians and acutely ill children and their parents, who were all left confused about the appropriate course of action to be taken in the face of such diametrically opposing views.

To address these issues, a group of clinicians and scientists were assembled in July 2010 for a workshop on "PANDAS". The quotation marks indicate that the discussions were not limited to cases meeting the five published criteria for the PANDAS cohort. In fact, the planning committee had elected to broaden the scope of the workshop to include all possible cases of acute-onset OCD, regardless of potential etiology. Primary tic disorders were not a topic of discussion, because of the reported difficulties in accurately identifying PANDAS among patients presenting with primary tic disorders (described above). In making these changes, the workshop organizers hoped not only to facilitate discussion of the broader spectrum of acute-onset OCD and related neuropsychiatric disorders, but also to aid in the development of descriptive criteria that could concisely summarize the clinical features distinguishing these patients.

From PANDAS to PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

Six clinicians (Drs. Elana Ben-Joseph, Boston MA; Josephine Elia, Philadelphia PA; Miroslav Kovacevic, Hinsdale IL; Elizabeth Latimer, Rockville MD; Tanya K. Murphy, Tampa FL; and Margo Thienemann, Palo Alto CA) presented clinical data extracted from their evaluations of more than 400 (total) children and adolescents who had been diagnosed with PANDAS. Each of the physicians summarized their patients' demographic information; clinical presentation at initial onset of symptoms and during subsequent exacerbations; and laboratory results. Specific details of the case reports are not presented here, but are comparable to those recently reported by Murphy and colleagues [42]. Several trends that had been observed in the first 50 cases in the PANDAS subgroup [1] were again apparent: boys outnumbered girls 2:1; symptom onset occurred most frequently before age 8 years; obsessive-compulsive symptoms were universally present; and comorbid neuropsychiatric symptoms were observed in more than 90% of patients.

On the basis of the clinical summaries, the conference participants were asked to identify the symptom or symptoms which best

characterized the collective group of patients. There was unanimous agreement that an "acute and dramatic symptom onset" was the key clinical feature. Particularly noteworthy were cases where parents had been able to identify the exact date and time that their children's symptoms had begun, and their descriptions of the onset as "ferocious", "overwhelming" or "severe enough that we took him to the ER". Acute onset was considered integral to the clinical presentation and was incorporated into one of the names proposed for this new clinical entity -- Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Childhood Acute-onset Neuropsychiatric Syndrome (CANS) was also proposed [41], but was not favored because "childhood" would exclude adolescents, while "pediatric" extends to at least age 18 years (and in some definitions, 21 years). Because adolescent cases were not uncommon in the clinicians' experience, the conference participants decided that the new syndrome should not exclude cases with post-pubertal onset, as the PANDAS criteria had done [1,43].

As shown in Figure 1, PANS is postulated to be much broader than PANDAS and PITANDS, including not only disorders potentially associated with a preceding infection, but also acute-onset neuropsychiatric disorders without an apparent environmental precipitant or immune dysfunction. Because cases of PANS are defined clinically, the syndrome is expected to include a number of related disorders which have different etiologies but share a common clinical presentation – the foudroyant (lightning-like) onset or recurrence of OCD which is accompanied by two or more co-occurring neuropsychiatric symptoms. The diagnostic criteria proposed for PANS are shown in Table 2.

Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake

"Abrupt, dramatic onset of OCD" is the first diagnostic criterion for PANS. The acuity of onset and initial severity of the OC symptoms are hallmarks of the diagnosis. The obsessive-compulsive symptoms must be sufficiently frequent and intense to meet DSM-IV criteria for OCD and must cause significant distress and interference in the child's activities at home, at school and with peers [44]. Although an acute

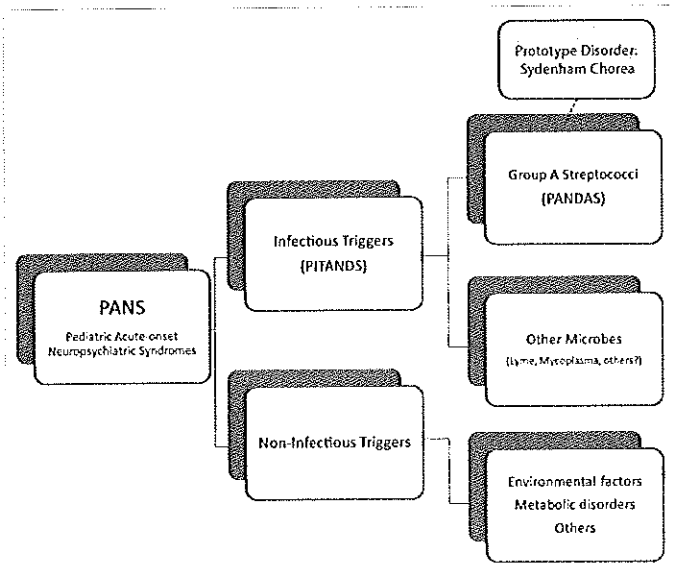


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Criterion	Description
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see text for full description):
	1. Anxiety
	2. Emotional lability and/or depression
	3. Irritability, aggression and/or severely oppositional behaviors
	4. Behavioral (developmental) regression
	5. Deterioration in school performance
	6. Sensory or motor abnormalities
	7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others.
	Note: The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

Table 2: Diagnostic Criteria Proposed for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

and dramatic onset of OCD is required for a PANS diagnosis, a prior history of mild, non-impairing obsessions or compulsions does not rule out the syndrome, as children may have had subclinical symptoms present for an extended period prior to the sudden onset of the full disorder.

In addition to the obsessions and compulsions typically manifest in childhood, the first PANS criterion may also be fulfilled by restricted food intake and abnormal eating behaviors. NIMH investigators had noted eating restrictions in their sample of SC patients [6-7], but Sokol and Gray [45-46] were the first to observe the acute onset of anorexia following untreated GAS infections. In some patients, body image distortions appeared to drive the weight-loss inducing behaviors; while in the majority, the body image distortions appeared only after the child had lost a significant amount of weight (10-15% of starting weight) as a result of food intake restrictions that were related to obsessional preoccupations with the texture of food and a fear of choking, vomiting or contamination from ingesting specific foods [6,7,45-46]. Subsequent reports have confirmed the significant symptom overlap between eating restrictions and OCD [47,48]. Thus, the working PANS criteria specify that the sudden onset of eating restrictions or anorexic behaviors can fulfill the first criterion, even in the absence of more typical symptoms of OCD.

Concurrent presence of at least two additional neuropsychiatric symptoms, with similarly severe and acute onset

The precipitous confluence of multiple neuropsychiatric symptoms is a second fundamental feature of PANS (see Criterion 2 in Table 2). The acuity and severity of symptom onset is such that parents will describe their children as "possessed" by the illness over the course of just a few days. Although there is uniformity in the acuity and severity of onset of the co-occurring symptoms, there is great variability in the type of symptoms that are manifest. For example, one child might have severe separation anxiety and developmental regression in association with his OCD, while another presents with new onset of motor tics, concentration difficulties and emotional lability. Further, a child's

symptom profile may evolve over time, with one set of symptoms predominating at onset and others becoming problematic after a period of days or weeks. To allow for this variability, the draft criteria for PANS list seven different categories of symptoms and allow any combination of symptoms from two or more categories. The categories of co-occurring symptoms include:

Anxiety: The anxiety may be manifest as de novo or suddenly exacerbated separation anxiety, generalized anxiety, irrational fears or worries, or a specific phobia. Early in the course of illness, the child may appear "terror stricken", hyper-alert and excessively vigilant, as if confronted by a constant threat of imminent danger. Over the course of a several days to a few weeks, the apparent panic may subside to a state of generalized anxiety, which might present with repeated requests for reassurance that the child didn't do something wrong or that he's safe. Children with separation anxiety may seek physical proximity, as well as reassurance about their safety. As the name implies, separation fears typically are focused on the health and safety of one or more loved ones, but in rare cases, they center on concerns about being parted from an inanimate object, such as a piece of furniture or a room in their home. The separation anxiety may become so severe that the child will insist on sleeping between his parents or staying within reach of his mother, even when she uses the restroom.

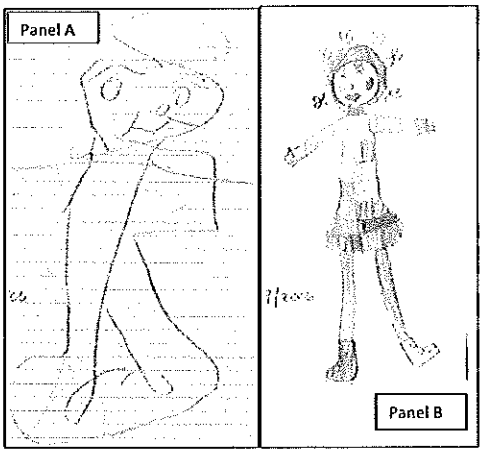
Emotional lability and depression : Emotionally labile children experience sudden and unexpected changes in mood states, often shifting from laughter to tears without obvious precipitant. The children may complain that they have an inner sense of restlessness and agitation, which is similarly unprecipitated and inexplicable. Some children may experience the abrupt onset of a clinical depression, which can become severe enough to be accompanied by suicidal ideation. Self-injurious behaviors and suicidal ideation are also common and are of particular concern among children with concomitant impulsivity and behavioral regression, as they may cause themselves serious injury.

Aggression, irritability and oppositional behaviors: These symptoms often top the list of parental concerns because they are so disruptive. The irritability and oppositional behaviors are present throughout the day and the aggression occurs without provocation or precipitant. Most notable is the striking contrast between these new behaviors and the child's usual state of being "sweet-tempered and well-behaved" or "easy-going and well-liked".

Outbursts occurring in response to interruption of an obsessional thought or compulsive ritual should not be counted as a manifestation of this category, as they are an expected occurrence among pediatric patients with severe OCD.

Behavioral (developmental) regression: The symptoms of developmental regression include an abrupt increase in temper tantrums, loss of age-appropriate language (sometimes to the point of the child using "baby talk"), and other behaviors inappropriate to the child's chronological age and previous stage of development. The developmental regression may be most apparent in the child's school assignments or artwork, as shown in Figure 2.

Sudden deterioration in school performance or learning abilities: A number of factors may contribute to the child's academic difficulties, including among others, a shortened attention span, difficulties with concentration or memorization, specific losses of math skills or visuospatial skills, and other disturbances of cognition or executive



Panel A– Drawing produced during an acute exacerbation of OCD and other symptoms of PANDAS which appears quite messy and immature.

Panel B – Age-appropriate picture drawn after treatment with IVIG and symptomatic improvement.

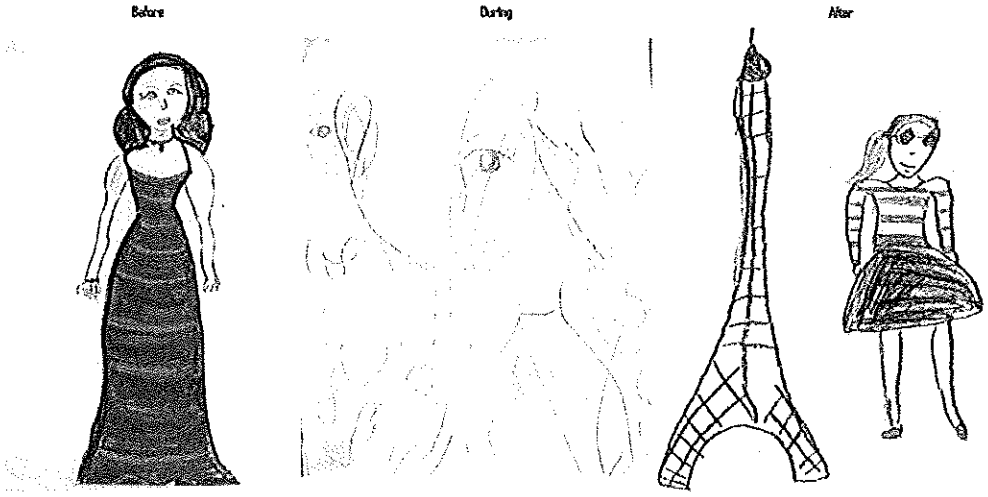
Figure 2: Handwriting Samples Showing Behavioral Regression During Symptomatic Episode.

functioning. As with the other categories, the academic difficulties must represent a distinct change from previous levels of functioning that occurs at the time of the onset of OCD symptoms. Thus, chronic manifestations of attention deficit hyperactivity disorder (ADHD) or a learning disability are not counted here, nor are the visuospatial and fine motor skill deficits that are commonplace in chronic tic disorders and classical childhood-onset OCD [49,50].

Sensory and motor abnormalities: The sensory abnormalities may include a sudden increase in sensitivity to light, noises, smells, tastes or textures of foods or items of clothing; or conversely, sensory seeking behaviors, such as needing to touch or feel particular objects or textures. Visual hallucinations may also occur and might include frightening images and perceptions that objects are floating or that they're larger or smaller than actual size. The visual hallucinations are usually brief and only mildly disturbing, but in severe cases, may be quite frightening and persistent, lasting for several hours or longer.

Motor abnormalities occurring in PANS include a variety of signs and symptoms, such as an abrupt deterioration of the child's handwriting (dysgraphia), clumsiness, motor hyperactivity, tics and choreiform movements. Dysgraphia is a particularly useful diagnostic feature, as handwriting samples obtained during the child's acute illness can be compared against those produced during an asymptomatic period to document the motor changes, (see Figure 3) or even to identify precipitating infections by comparing longitudinally collected handwriting samples with infections documented in the child's medical record [51]. Choreiform movements must be distinguished from the choreatic movements of Sydenham chorea. While chorea is characterized by jerky or writhing, arrhythmic involuntary movements of the extremities, trunk and facial muscles, choreiform movements are described as "fine, piano-playing movements of the fingers" that are present only when the child maintains stressed postures such as a Romberg stance [52].

Somatic signs and symptoms: Sleep problems and disturbances of urination and micturation are among the most common physical manifestations of PANS. The sleep disturbances may include not



Handwriting samples documenting dysgraphia during acute illness.

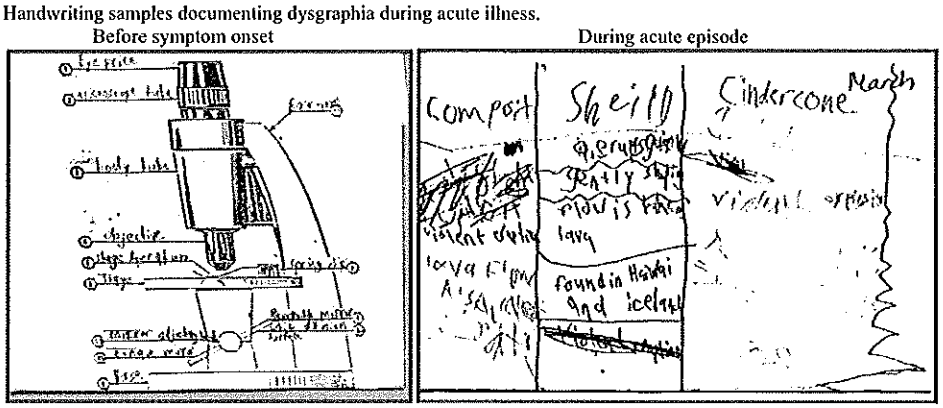


Figure 3: Drawings that Demonstrate Loss of Fine Motor Skills During Acute Illness.

only the new onset of terrifying nightmares and night terrors, but also difficulties falling asleep, staying asleep or waking up too early (early, middle or terminal insomnia). To avoid double-counting sleep disturbances, it is important to ensure that they're not a manifestation of an anxiety disorder. Urinary symptoms are often the presenting complaint for children with PANDAS. A pediatric clinic-based case series reported that 7 of 12 PANDAS patients initially presented with urinary symptoms, including the new onset of night-time bedwetting (secondary enuresis), daytime urinary frequency, and an urgency to void, without evidence of urinary tract infection [53]. Subsequent experience has confirmed that urinary symptoms occur frequently during recurrences, as well as at the onset of symptoms. The symptoms are occasionally related to obsessional concerns with toileting or contamination fears, but for most children, no cognitive or emotional explanation can be found.

Symptoms are not better explained by a known neurologic or medical disorder

The third major criterion for PANS requires that "Symptoms are not better explained by a known neurological or medical disorder, such as SC, systemic lupus erythematosus, Tourette disorder, or others." Thus, to make a diagnosis of PANS, clinicians must perform a diagnostic evaluation that is comprehensive enough to rule out all other disorders, including toxic effects of drugs or medications, acute disseminated encephalomyelitis, and other neurologic disorders. A complete medical history and thorough physical and neurological examination is usually sufficient to exclude the possibility of SC and many other neurological disorders. The remainder of the diagnostic evaluation should be guided by the presenting signs and symptoms, and might include laboratory tests on blood and cerebrospinal fluid, an electroencephalogram, MRI scan, or other diagnostic tests, as indicated. In addition, it may be useful to obtain a throat culture for GAS or serial antibody titers, or to perform other laboratory tests that might identify a treatable precipitant for the neuropsychiatric symptoms.

Use of the PANS Criteria

The goal of the new PANS criteria is to attempt to define the clinical presentation of a relatively narrow group of patients in order to improve the comparability of research samples. Given the breadth of potential etiologies for PANS, it will be essential for its clinical presentation to be as uniform and homogeneous as possible. The current criteria were based on the presentations commonly seen in moderately to severely affected patients with acute-onset OCD and admittedly may exclude children with only mild symptom severity or those with an atypical presentation. Excluding such cases was considered preferable to broadening the criteria to include all borderline cases, as that was likely

to introduce extraneous patient groups and further complicate the search for common disease mechanisms for PANS. During the process of refining the diagnostic criteria for PANS, it will be helpful to learn about cases in which a child "almost met" the PANS criteria but could not be included because of variances from the published description. Atypical presentations also will be of interest and may be helpful in determining the clinical boundaries of the syndrome.

The proposed criteria should be considered as "working criteria", which will undergo modifications and refinement as additional clinical and research experience is accrued. To aid in this effort, it is essential that the clinical features of PANS are described in such a way that between-site comparisons can be made. A PANS diagnostic and assessment tool is currently under development at Yale University to provide a reliable and valid means of standardizing the diagnostic evaluation of children suspected of having PANS.

Summary and Future Directions

A set of criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) has been proposed in order to identify a unique and homogenous group of patients who share key clinical characteristics, including the fulminant onset of obsessive-compulsive symptoms and a multiplicity of co-occurring signs and symptoms. The draft criteria must now be validated through careful, systematic application in clinical practice and research investigations. Systematic clinical observations are needed in order to learn more about the clinical characteristics, natural and treated history, and prognosis of PANS, as well as to identify potential precipitants of symptom onset and exacerbations. Research investigations are required to evaluate the validity, reliability and utility of the draft criteria, as well as to evaluate potential etiologic factors and mechanisms of disease that might be common to the disorders subsumed under the PANS clinical description.

To achieve those objectives, a number of immediate and longer term research studies are required. Large-scale epidemiologic studies and a centralized registry are needed to evaluate the sensitivity and specificity of the draft criteria for PANS and to characterize the incidence, prevalence and demographics of the syndrome. These community-based studies may also serve to identify environmental risk factors and precipitants, just as epidemiologic efforts were critical to the discovery that cigarette smoking causes lung cancer and heart disease. Unfortunately, such large scale epidemiologic investigations are likely to be prohibitively expensive, as the accurate diagnosis of PANS currently requires the investment of sufficient amounts of time to allow interviewers to obtain a detailed description of the onset and course of the neuropsychiatric symptoms, comprehensive medical and family histories, and information about a wide variety of environmental factors that might put a child at risk for PANS or trigger the onset or worsening of the neuropsychiatric symptoms. While chart reviews and other retrospective methodologies may be useful in narrowing the scope of the prospective investigations, they cannot provide the data needed to definitively establish an etiological role for a proposed trigger or set of environmental precipitants. Ideally, biomarkers identifying at-risk and affected individuals will be developed that can be utilized in the epidemiologic studies to accurately separate cases from controls.

In addition to the community-based studies, research on PANS should include a wide variety of clinical, translational and basic science investigations. The studies should build on the past two decades of research on PANDAS by applying those findings to the larger cohort of patients with PANS. For example, animal models recently demonstrated that GAS infections can trigger the production of cross-reactive antibodies that not only induce neurologic and behavioral symptoms in the originally infected mice, but also evoke symptoms when passively transferred to donor mice [54-55]. Expanding these investigations to evaluate the effects of a variety of infectious agents and other immune stimulants would be useful, particularly if the animal models can be used to evaluate potential therapeutic interventions. Investigations of other neuroimmune disorders, such as systemic lupus erythematosus, may also provide insights into the disease mechanisms underlying the OC symptomatology in PANS [56]. As research on PANS progresses, close collaborations between basic and clinical scientists will ensure that laboratory findings are translated rapidly into clinical practice through the development of new and more effective therapeutic and preventive interventions.

While waiting for the results of those research investigations, clinicians are encouraged to consider PANS when children present with acute-onset of obsessive-compulsive symptoms, separation anxiety or emotional lability. Because OCD is a disorder of "rational irrationality", affected children often recognize the absurdity of their obsessional thoughts and compulsive rituals and will not volunteer information about the content of their OCD symptoms; they may also downplay the severity of their distress. In such cases, standardized instruments, such as the Children's Yale-Brown Obsessive-Compulsive Scale [57], can be useful in documenting the nature and extent of the child's symptoms.

PANS should also be included in the differential diagnosis of secondary enuresis or daytime urinary frequency (after ruling out a urinary tract infection), and when an older child abruptly develops motoric hyperactivity, handwriting deterioration, or academic difficulties. If the child fulfills the clinical criteria for PANS, the possibility of PANDAS should also be considered and appropriate laboratory studies obtained to determine if GAS played a role in the etiology of the child's symptoms. Depending on the child's history and physical examination, other infectious triggers might also be considered and appropriate laboratory studies obtained. In children for whom no etiologic trigger can be identified, therapeutic interventions for PANS are limited to symptomatic treatments, including medications and behavioral therapies. Standard therapeutic approaches are often helpful, including use of an SSRI for obsessive-compulsive symptoms or an anti-dopaminergic medication for tics. However, treating clinicians must "Start Low and Go Slow!" as children with acute-onset neuropsychiatric disorders are exquisitely sensitive to psychotropic medications [42]. Supportive therapies also may be indicated, as the symptoms of PANS can be distressing not only to the affected child, but also to his parents or caregivers.

References

1. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, et al. (1998) Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 155: 264-271.

2. Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D (1989) Obsessive-compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 46: 335-341.

3. Swedo SE, Rapoport JL, Cheslow DL, Leonard HL, Ayoub EM, et al. (1989) High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. Am J Psychiatry 146: 246-249.

4. Swedo SE, Leonard HL, Kiessling LS (1994) Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics 93: 323-326.

5. Allen AJ, Leonard HL, Swedo SE (1995) Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 34: 307-311.

6. Swedo SE, Leonard HL, Schapiro MB, Casey BJ, Mannheim GB, et al. (1993) Sydenham's chorea: physical and psychological symptoms of St Vitus dance. Pediatrics 91: 706-713.

7. Swedo SE (1994) Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disorders. JAMA 272: 1788-1791.

8. Garvey MA, Giedd J, Swedo SE (1998) PANDAS: the search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. J Child Neurol 13: 413-423.

9. Murphy TK, Goodman WK, Ayoub EM, Voeller KK (2000) On defining Sydenham's chorea: where do we draw the line? Biol Psychiatry 47: 851-857.

10. Mercadante MT, Busatto GF, Lombroso PJ, Prado L, Rosário-Campos MC, et al. (2000) The psychiatric symptoms of rheumatic fever. Am J Psychiatry 157: 2036-2038.

11. Asbahr FR, Garvey MA, Snider LA, Zanetta DM, Etkis H, et al. (2005) Obsessive-compulsive symptoms among patients with Sydenham chorea. Biol Psychiatry 57: 1073-1076.

12. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW (2003) Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat Med 9: 914-920.

13. Kirvan CA, Swedo SE, Kurahara D, Cunningham MW (2006) Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. Autoimmunity 39: 21-29.

14. Kirvan CA, Swedo SE, Snider LA, Cunningham MW (2006) Antibody-mediated neuronal cell signaling in behavior and movement disorders. J Neuroimmunol 179: 173-179.

15. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW (2007) Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol 178: 7412-7421.

16. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, et al. (1999) Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 354: 1153-1158.

17. Garvey MA, Snider LA, Leitman SF, Werden R, Swedo SE (2005) Treatment of Sydenham's chorea with intravenous immunoglobulin, plasma exchange, or prednisone. J Child Neurol 20: 424-429.

18. Berrios X, Quesney F, Morales A, Blazquez J, Bisno AL (1985) Are all recurrences of "pure" Sydenham chorea true recurrences of acute rheumatic fever? J Pediatr 107: 867-872.

19. Kurlan R, Johnson D, Kaplan EL; and the Tourette Syndrome Study Group (2008) Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. Pediatrics 121: 1188-1197.

20. Lin H, Williams KA, Katsovich L, Findley DB, Grantz H, et al. (2010) Streptococcal upper respiratory tract infections and psychological stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. Biological Psychiatry 67: 684-691.

21. Snider LA, Sachdev V, MaCkaronis JE, St Peter M, Swedo SE (2004) Echocardiographic findings in the PANDAS subgroup. Pediatrics 114: e748-751.

22. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, et al. (2009) Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. Circulation 119: 1541-1551.

23. Garvey MA, Perlmutter SJ, Allen AJ, Hamburger S, Lougee L, et al. (1999) A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry 45: 1564-1571.

24. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE (2005) Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry 57: 788-792.

25. Müller N, Riedel M, Blendinger C, Oberle K, Jacobs E, et al. (2004) Mycoplasma pneumoniae infection and Tourette's syndrome. Psychiatry Res 129: 119-125.

26. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G (2008) Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. J Child Neurol 23: 338-340.

27. Schneider RK, Robinson MJ, Levenson JL (2002) Psychiatric presentations of non-HIV infectious diseases. Neurocysticercosis, Lyme disease, and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection. Psychiatr Clin North Am 25: 1-16.

28. Gabbay V, Coffey BJ, Babb JS, Meyer L, Wachtel C, et al. (2008) Pediatric autoimmune neuropsychiatric disorders associated with streptococcus: comparison of diagnosis and treatment in the community and at a specialty clinic. Pediatrics 122: 273-278.

29. Shulman ST (2009) Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS): update. Curr Opin Pediatr 21: 127-130.

30. Kaplan EL, Rothermel CD, Johnson DR (1998) Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. Pediatrics 101: 86-88.

31. Wessels MR (2011) Clinical practice. Streptococcal pharyngitis. N Engl J Med 364: 648-655.

32. Johnson DR, Kurlan R, Leckman J, Kaplan EL (2010) The human immune response to streptococcal extracellular antigens: clinical, diagnostic, and potential pathogenetic implications. Clin Infect Dis 50: 481-490.

33. Tsunoda I, Libbey JE, Fujinami RS (2007) Sequential polymicrobial infections lead to CNS inflammatory disease: possible involvement of bystander activation in heterologous immunity. J Neuroimmunol 188: 22-33.

34. Leckman JF, King RA, Gilbert DL, Coffey BJ, Singer HS, et al. (2011) Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: a prospective longitudinal study. J Am Acad Child Adolesc Psychiatry 50: 108-118.

35. Mink J, Kurlan R (2011) Acute postinfectious movement and psychiatric disorders in children and adolescents. J Child Neurol 26: 214-217.

36. Singer HS, Gause C, Morris C, Lopez P; Tourette Syndrome Study Group (2008) Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Pediatrics 121: 1198-1205.

37. Murphy TK, Kurlan R, Leckman J (2010) The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with Streptococcus, and related disorders: a way forward. J Child Adolesc Psychopharmacol 20: 317-331.

38. Kurlan R (1998) Tourette's syndrome and 'PANDAS': will the relation bear out? Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Neurology 50: 1530-1534.

39. Kurlan R, Kaplan EL (2004) The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. Pediatrics 113: 883-886.

40. Kurlan R (2004) The PANDAS hypothesis: losing its bite? Mov Disord 19: 371-374.

41. Singer HS, Gilbert DL, Wolf DS, Mink JW, Kurlan R (2011) Moving from PANDAS to CANS. J Pediatr .

42. Murphy TK, Storch EA, Lewin AB, Edge PJ, Goodman WK (2012) Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Pediatr 160: 314-319.

43. Swedo SE, Leonard HL, Rapoport JL (2004) The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) subgroup: separating fact from fiction. Pediatrics 113: 907-911.

44. Frances A, Pincus HA, First MB (2000) American Psychiatric Association, Diagnostic and statistical manual of mental disorders (4thedn), American Psychiatric Association, Washington, DC.

45. Sokol MS, Gray NS (1997) Case study: an infection-triggered, autoimmune subtype of anorexia nervosa. J Am Acad Child Adolesc Psychiatry 36: 1128-1133.

46. Sokol MS (2000) Infection-triggered anorexia nervosa in children: clinical description of four cases. J Child Adolesc Psychopharmacol 10: 133-145.

47. Harel Z, Hallett J, Riggs S, Vaz R, Kiessling L (2001) Antibodies against human putamen in adolescents with anorexia nervosa. Int J Eat Disord 29: 463-469.

48. Vincenzi B, O'Toole J, Lask B (2010) PANDAS and anorexia nervosa--a spotters' guide: suggestions for medical assessment. Eur Eat Disord Rev 18: 116-123.

49. Bloch MH, Sukhodolsky DG, Leckman JF, Schultz RT (2006) Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. J Child Psychol Psychiatry 47: 551-559.

50. Bloch MH, Sukhodolsky DG, Dombrowski PA, Panza KE, Craiglow BG, et al. (2011) Poor fine-motor and visuospatial skills predict persistence of pediatric-onset obsessive-compulsive disorder into adulthood. J Child Psychol Psychiatry 52: 974-983.

51. Snider LA, Seligman LD, Ketchen BR, Levitt SJ, Bates LR, et al. (2002) Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. Pediatrics 110: 331-336.

52. Touwen B (1979) Examination of the Child with Minor Neurological Dysfunction. (2ndedn), London: Clinics in Developmental Medicine 53.

53. Murphy ML, Pichichero ME (2002) Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med 156: 356-361.

54. Hoffman KL, Hornig M, Yaddanapudi K, Jabado O, Lipkin WI (2004) A murine model for neuropsychiatric disorders associated with group A beta-hemolytic streptococcal infection. J Neurosci 24: 1780-1791.

55. Yaddanapudi K, Hornig M, Serge R, De Miranda J, Baghban A, et al. (2010) Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Mol Psychiatry 15:712-726.

56. Slattery MJ, Dubbert BK, Allen AJ, Leonard HL, Swedo SE, et al. (2004) Prevalence of obsessive-compulsive disorder in patients with systemic lupus erythematosus. J Clin Psychiatry 65: 301-306.

57. Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, et al. (1997) Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 36: 844-852.

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The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (PANDAS) Subgroup: Separating Fact From Fiction

Susan E. Swedo, Henrietta L. Leonard and Judith L. Rapoport

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COMMENTARIES

Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (PANDAS) Subgroup: Separating Fact From Fiction

ABBREVIATIONS. OCD, obsessive-compulsive disorder; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; NIMH, National Institute of Mental Health.

Over a century ago, Sir William Osler wrote, "To carefully observe the phenomena of life in all its phases . . . to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false—these are our methods."[1]

These were also the methods that led to the discovery of poststreptococcal obsessive-compulsive disorder (OCD) and tic disorders and a decade of observations and research resulting in the description of a novel cohort of patients, the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) subgroup.[2,3] In this issue of *Pediatrics*, Kurlan and Kaplan raise questions about the veracity of these data.[4] To respond, we will provide a brief literature review and clarification of the guidelines for management of a patient in the PANDAS subgroup.

The discovery of the PANDAS subgroup was the result of 2 parallel lines of clinical research conducted at the National Institute of Mental Health (NIMH): studies of children with OCD and investigations of children with Sydenham's chorea, the neurologic manifestation of rheumatic fever. Systematic observations of children with OCD revealed that, although the majority of children had a gradual onset of symptoms over several weeks to months, a subgroup of the patients experienced an explosive "overnight" onset of obsessions and compulsions followed by a relapsing-remitting symptom course.[5] Closer observation revealed that the neuropsychiatric symptom relapses frequently occurred after episodes of streptococcal pharyngitis or scarlet fever. These findings in OCD closely paralleled those from a series of investigations of Sydenham's chorea.[6] In those studies, 65% to 100% of children with Sydenham's chorea were noted to have obsessive-compulsive symptoms, typically presenting 2 to 4 weeks before the onset of the adventitious movements and peaking in severity simultaneously with the chorea.[6,7] Longitudinal observations of the OCD subgroup and the patients with Sydenham's chorea clearly demonstrated a temporal association between streptococcal infections and obsessive-compulsive symptoms. This relationship was not only observed consistently among patients presenting to the NIMH but also noted by several independent groups.[8–11] The nature of the association was unknown, and the observations could not elucidate whether the streptococcal infections played an etiologic role, but these issues would be addressed through subsequent scientific experimentation.

The title of the article by Kurlan and Kaplan[4] provides a provocative starting point for discussion of the scientific hypotheses that derive from the clinical observations of the PANDAS subgroup. However, the authors subsequently blur the distinction between clinical observation and scientific investigation, leading them to dismiss the well-documented observations that neuropsychiatric symptoms are associated with streptococcal infections in the PANDAS subgroup because the etiology of PANDAS "remains a yet-unproven hypothesis."[4] The authors thus recommend against obtaining throat cultures or serial titers in patients with abrupt-onset OCD and tics "until more definitive scientific proof is forthcoming." We strongly disagree with this recommendation. The continued threat of rheumatic fever mandates the detection and appropriate treatment of streptococcal infections, including asymptomatic infections, the leading cause of rheumatic carditis in the United States.[12] If one argues that OCD and tics are a manifestation of streptococcal infection for children in the PANDAS subgroup, then the infections aren't really "silent" or "asymptomatic." In either case, a conservative treatment course would include administration of antibiotics for culture-proven streptococcal infections. In addition, Murphy and Pichichero[11] have documented that prompt treatment of streptococcal infections is associated with a rapid diminution of obsessive-compulsive symptom severity for some children in the PANDAS subgroup. Thus, the potential benefits of appropriate diagnosis and treatment of an occult streptococcal infection far outweigh the modest cost of obtaining a throat swab and culture. Of course, when throat cultures are obtained, there is a risk of falsely identifying a "carrier" as an asymptomatic infection, but this risk is small. Systematic studies typically report the frequency of

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carriers to be <5% to 10%.[13] Thus, the vast majority of positive throat cultures represent true streptococcal infections, for which antibiotics administration is the accepted standard of care.

CLINICAL CRITERIA

Kurlan and Kaplan contend that the 5 criteria defining the PANDAS subgroup are not "particularly useful in distinguishing patients suspected of PANDAS from children with more typical cases of TS [Tourette's syndrome] or OCD."[4] In actuality, the criteria have been used successfully by a variety of clinical groups to define cohorts of patients with common clinical characteristics and a predictable clinical course.[3,9–11,14] This had been the original purpose of describing the PANDAS subgroup: to enable investigators to identify a clinically homogeneous group of patients for inclusion in research studies at the NIMH and elsewhere. Subsequent investigations have demonstrated that the criteria have clinical utility as well, in that they define a distinct cohort of patients who are uniquely responsive to novel therapeutic interventions and prevention strategies. The following is a clarification of the criteria.

The Presence of a Tic Disorder and/or OCD

The symptom characteristics and severity required for diagnosis are defined in the *Diagnostic and Statistical Manual of Mental Disorders*.[15] The neuropsychiatric symptoms of the PANDAS subgroup were intentionally limited to tics and obsessive-compulsive symptoms because of our interest in establishing a homogeneous patient cohort for research studies. Subsequent interest in the PANDAS subgroup has sparked a number of authors to speculate that the criteria should be expanded to include other related disorders such as attention-deficit/hyperactivity disorder[16] and anorexia.[17] However, such a change requires systematic evidence documenting that the association between streptococcal infections and symptom onset in these disorders is not merely a chance finding; to date, such systematic studies have not been done.

Prepubertal Age at Onset, Usually Between 3 and 12 Years of Age

This criterion was based on historical data demonstrating that rheumatic fever and other poststreptococcal sequelae are uncommon before the age of 3 years and after the age of 12 years.[18] Fischetti[19] provides a possible explanation for the rarity of postpubertal sequelae of streptococcal infections and demonstrated the presence of serum antibodies conferring protection against streptococcal infections in 98% of healthy 12-year-old controls, making it unlikely that poststreptococcal neuropsychiatric symptoms would have their initial presentation after this age. Thus, we set the age range for the PANDAS subgroup at a point that had biological relevance and would include 98% of the cases.

Abrupt Symptom Onset and/or Episodic Course of Symptom Severity

Prospective longitudinal investigations have demonstrated that this criterion is the most useful in identifying children in the PANDAS subgroup.[2,3,9–11] Contrary to the concerns expressed by Kurlan and Kaplan,[4] the abrupt onset of tics in the PANDAS subgroup is clearly different from the typical onset of an isolated, intermittent, simple motor or vocal tic, because children in the PANDAS subgroup experience the simultaneous onset of several different motor and vocal tics of such intensity and frequency that emergency treatment is often sought.[14] PANDAS-related OCD is also easily distinguished from non-PANDAS OCD, because the latter patients have a slow, gradual symptom onset, whereas children in the PANDAS subgroup have an overnight "explosion" of obsessive-compulsive symptoms, reaching maximal, clinically significant impairment in 24 to 48 hours.[3,20]

The episodic, relapsing-remitting course of the PANDAS subgroup is distinctly different from the undulating, waxing-waning course seen in other patients with OCD or tic disorders.[20,21] When the symptoms of a child in the PANDAS subgroup are graphed against time, a "saw-toothed" pattern emerges, in which periods of symptom quiescence are interrupted abruptly by severe symptom exacerbations; these relapses typically take several weeks to months to resolve. Prospective, longitudinal evaluation of these patients allows for documentation of the relationship between the symptom exacerbations and streptococcal infections: throat cultures obtained at the beginning of a symptom relapse will be positive, and titers obtained at baseline and 4 to 6 weeks later will demonstrate a clinically significant rise.

Temporal Association Between Symptom Exacerbations and Streptococcal Infections

Although it was postulated initially that there could be a significant time lag between the inciting streptococcal infection and the presentation of the neuropsychiatric sequelae (such as that seen in Sydenham's chorea),[6] clinical observations of the PANDAS subgroup revealed that the window is actually much narrower. Exacerbations of neuropsychiatric symptoms begin within 7 to 14 days after the streptococcal infection and usually occur simultaneously (ie, a throat culture obtained because of the recent onset of OCD and/or tics is positive).[3,11,20,21]

One caveat in evaluating the relationship between streptococcal infections and neuropsychiatric symptoms is that the disorders are so common that cooccurrence can be a random coincidence rather than a clinically significant finding. OCD occurs in 1% to 2% of school-aged children, and transient motor tics occur in as many as 10% to 25% of early elementary students.[22,23] Furthermore, during regional streptococcal epidemics, the majority of children will be infected at least once during the outbreak.[13] Thus, as discussed in our original report,[3] a single positive throat culture or elevated antistreptococcal antibody titer is not sufficient to determine that a child's neu-

ropsychiatric symptoms are associated with streptococcal infections.[3,20] Instead, the determination that a child fits the PANDAS profile is made through prospective evaluation and documentation of the presence of streptococcal infections in conjunction with at least 2 episodes of neuropsychiatric symptoms, as well as demonstrating negative throat culture or stable titers during times of neuropsychiatric symptom remission.[3] A child who has multiple symptom exacerbations without evidence of streptococcal infection would not be considered part of the PANDAS subgroup, nor would a child who has numerous streptococcal infections without subsequent symptom exacerbations.

Presence of Neurologic Abnormalities During Periods of Symptom Exacerbation

Neurologic examination of acutely ill children in the PANDAS subgroup reveals that 95% have choreiform movements.[3] These fine piano-playing movements of the fingers are not easily confused with the writhing adventitious movements of Sydenham's chorea.[24] Choreiform movements are not present at rest and must be elicited through stressed postures, whereas choreatic movements are present continuously and increase with unrelated voluntary movements. In addition, choreiform movements are an isolated finding, whereas the choreatic movements of Sydenham's chorea are accompanied by a failure to sustain tetanic contractions (milk-maid's grip, snake-like tongue) and muscle weakness.[6,18] Choreiform movements and chorea may share a common pathophysiology (related to dysfunction of the basal ganglia), but the clinical manifestations are quite distinct, and children in the PANDAS subgroup do not represent missed cases of Sydenham's chorea. In fact, rheumatic fever, including Sydenham's chorea, is a strict exclusionary criterion for the PANDAS subgroup.[3]

SCIENTIFIC HYPOTHESES

Clinical observations of the PANDAS subgroup led to a number of scientific hypotheses including the postulate that the tics and OCD represent sequelae of group A streptococcal infections. This etiologic hypothesis involves a series of factors including pathologic strains of group A streptococcal bacteria, host susceptibility (genetic, developmental, or other), and abnormal immune responsivity (Fig 1). The working model of pathogenesis not only provides a framework for understanding the etiology of OCD and tic disorders but also allows for the development of novel intervention and prevention strategies. A recent review provides a detailed description of the model as well as ongoing research efforts directed at understanding the pathologic mechanisms involved in the PANDAS subgroup.[25]

CLINICAL RECOMMENDATIONS

These guidelines are drawn from our clinical and research experience as well as the practice parameters of the American Academy of Child and Adolescent Psychiatry.[26]

1. Laboratory testing: Children with an abrupt onset or exacerbation of OCD or tic disorder should have a throat culture obtained. If the symptoms have been present for >1 week, serial antistreptococcal titers may be indicated to document a preceding streptococcal infection. (Titers should be timed to catch the rise at 4–6 weeks.)
2. Use of antibiotics: Antibiotics are indicated only for the treatment of acute streptococcal infections as diagnosed by a positive throat culture or rapid streptococcal test. Clinical trials are underway to determine whether prophylactic antibiotics will be useful in the management of children in the PANDAS subgroup, but at present, they are not indicated. In the only placebo-controlled trial reported to date, penicillin administration failed to prevent streptococcal infections (14 of 35 infections occurred during the penicillin phase of the crossover trial), and thus there were no between-group differences in neuropsychiatric symptom severity.[27]
3. Management of neuropsychiatric symptoms: Children in the PANDAS subgroup respond to treatment with standard pharmacologic and behavioral therapies. Obsessive-compulsive symptoms are treated best with a combination of medication

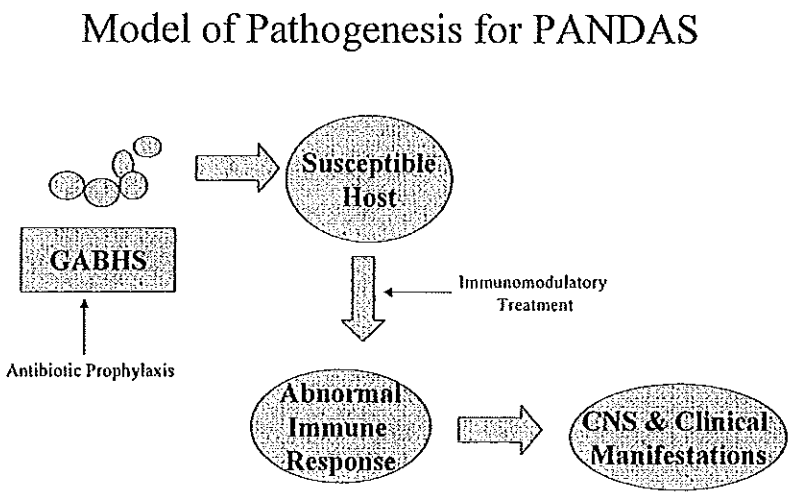

Fig 1. Model of pathogenesis for PANDAS.

(typically, a serotonin reuptake-blocking drug) and cognitive-behavior therapy, and motor and vocal tics respond to a variety of pharmacologic agents.

4. Immunomodulatory therapies: A randomized, placebo-controlled trial of intravenous immunoglobulin and therapeutic plasma exchange demonstrated significant and persistent improvements for a group of 29 severely affected children meeting criteria for the PANDAS subgroup.[28] The specificity of their response was demonstrated through a subsequent open-label trial of plasma exchange, which failed to produce benefits among children not meeting the PANDAS criteria.[29] After the publication of these reports, the American Society for Apheresis ranked therapeutic plasma exchange for poststreptococcal OCD and tic disorders "acceptable as second-line therapy or as an adjunct to primary therapy based on controlled trials."[30] Thus, immunomodulatory therapy may be a consideration for acutely and severely affected children in the PANDAS subgroup. Clinicians considering such an intervention are invited to contact the PANDAS research group at the NIMH for consultation.

CONCLUSIONS

The PANDAS subgroup is both a clinical entity and the subject of scientific experimentation. Systematic, longitudinal observations have demonstrated that the PANDAS subgroup has a distinct clinical presentation and an identifiable course of symptoms and that, for these children, there is a clear relationship between streptococcal infections and neuropsychiatric symptom exacerbations. Additional research is required to determine the nature of that relationship as well as to determine the etiopathogenesis of the poststreptococcal obsessive-compulsive symptoms and tics. Additional studies are required also to determine the role of immunomodulatory therapies and antibiotics prophylaxis for this group of patients. Meanwhile, it is time to end the debate about the existence of the PANDAS subgroup and begin to "call to aid the science of experimentation . . . so as to be able to know the true from the false."

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REFERENCES

1. Osler W. *Aphorisms From His Bedside Teachings and Writings*. Bean WB, ed. Springfield, IL: Charles C. Thomas, 1968
2. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1995;34:307–311
3. Swedo SE, Leonard HL, Garvey MA, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155:264–271
4. Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*. 2004;113:883–886
5. Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D. Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. *Arch Gen Psychiatry*. 1989;46:335–341
6. Swedo SE. Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. *JAMA*. 1994;272:1788–1791
7. Asbahr FR, Negrao AB, Gentil V, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. *Am J Psychiatry*. 1998;155:1122–1124
8. Murphy TK, Petitto JM, Voeller KK, Goodman WK. Obsessive compulsive disorder: is there an association with childhood streptococcal infections and altered immune function? *Semin Clin Neuropsychiatry*. 2001; 6:266–276
9. Tucker DM, Leckman JF, Scahill L, et al. A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1684–1691
10. Giulino L, Gammon P, Sullivan K, et al. Is parental report of upper respiratory infection at the onset of obsessive-compulsive disorder suggestive of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection? *J Child Adolesc Psychopharmacol*. 2002;12: 157–164
11. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med*. 2002;156:356–361
12. Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the United States. *J Pediatr*. 1994;124:9–16
13. Shulman ST. Streptococcal pharyngitis: clinical and epidemiologic factors. *Pediatr Infect Dis J*. 1989;8:816–819
14. Church AJ, Dale RC, Lees AJ, Giovannoni G, Robertson MM. Tourette's syndrome: a cross-sectional study to examine the PANDAS hypothesis. *J Neurol Neurosurg Psychiatry*. 2003;74:602–607
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth ed. Washington, DC: American Psychiatric Association; 1994
16. Peterson BS, Leckman JF, Tucker D, et al. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch Gen Psychiatry*. 2000;57:364–372
17. Sokol MS. Infection-triggered anorexia nervosa in children: clinical description of four cases. *J Child Adolesc Psychopharmacol*. 2000;10: 133–145
18. Stollerman GH. *Rheumatic Fever and Streptococcal Infection*. New York, NY: Grune & Stratton Inc; 1975
19. Fischetti V. The Streptococcus and the host. Present and future challenges. *Adv Exp Med Biol*. 1997;418:15–20
20. Perlmutter SJ, Garvey MA, Castellanos X, et al. A case of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Am J Psychiatry*. 1998;155:1592–1598
21. Snider L, Swedo S. Pediatric obsessive-compulsive disorder. *JAMA*. 2000;284:3104–3106
22. Zohar AH. The epidemiology of obsessive-compulsive disorder in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 1999;8:445–460
23. Snider LA, Seligman LD, Ketchen BR, et al. Tic and problem behaviors in school children: prevalence, characterization, and associations. *Pediatrics*. 2002;110:331–336
24. Touwen BCL. Examination of the child with minor neurological dysfunction. In: *Clinics in Developmental Medicine*. Vol. 71. London, United Kingdom: Heinemann; 1979:53
25. Swedo SE. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *Mol Psychiatry*. 2002;7(suppl 2):S24–S25
26. Practice parameters for the assessment and treatment of children and

adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1999;38:499–500
27. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry*. 1999;45:1564–1571
28. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet*. 1999;354:1153–1158
29. Nicolson R, Swedo SE, Lenane M, et al. An open trial of plasma exchange in childhood-onset obsessive-compulsive disorder without post-streptococcal exacerbations. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1313–1315
30. Weinstein R. A period of trial in American apheresis medicine. *Transfusion Apheresis Sci*. 2001;25:89–91

Navigating the Recent Articles on Girls' Puberty in *Pediatrics*: What Do We Know and Where Do We Go from Here?

ABBREVIATIONS. PROS, Pediatric Research in Office Settings; NHANES, National Health and Nutrition Examination Survey; NHES, National Health Examination Survey.

After the publication of the Pediatric Research in Office Settings (PROS) study on the age of onset of pubertal characteristics and menses in US girls in 1997,[1] a spate of related articles have appeared on emerging questions and controversies over recent pubertal data and the implications of these findings for clinical practice. The purpose of this commentary is to 1) summarize the consistencies and contradictions among some of these newer communications, 2) address misconceptions and misinterpretations of the PROS data, and 3) identify legitimate points of disagreement and areas for additional investigation.

A survey of just some of the recent articles demonstrates the scope of additional research both in our country and abroad.[2–17] The 1997 PROS study, a convenience sample of 17 077 white and black girls seen in pediatric practices across the United States and Puerto Rico used the Tanner method[18] to describe the ages of onset of breast development, pubic hair growth, and menarche. It found that the mean ages for these characteristics varied significantly between white and black girls (with black girls being at younger ages), the median age of menarche for black girls had dropped over the past several decades, and the ages for the onset of development seemed to be earlier than previous US studies as well as Marshall and Tanner's classic 1969 study.[18] The PROS study pointed out that the prevalence of secondary sexual characteristics in girls <8 years old was substantially higher than what had been believed previously and "that more appropriate standards for defining delayed and precocious puberty may need to be developed, that the timing of sex education in the schools may need revision, and that the etiology and effects require further study." The authors stated, "The findings of this study need to be confirmed in other research including a nationally representative sample such as HANES [Health and Nutrition Examination Survey]."[1] After the PROS study, Kaplowitz et al[2], using its data, provided additional analyses and new recommendations calling for the age for referral for precocious puberty to be lowered.

Between October 2002 and April 2003, *Pediatrics* alone has published 10 articles on puberty markers or issues.[19–28] Several of these articles beg for comment, in particular the articles that propose changes in practice or present interpretations of findings that contradict those of other recent articles. Six of the articles have been based wholly or in part on the most recent National Health and Nutrition Examination Survey (NHANES) data, and some present overlapping results or conflicting conclusions.[20,21,23–25,28]

The October 2002 article by Wu et al[20] analyzed data from the NHANES to report on ethnic differences in secondary sexual characteristics and menarche. The authors presented mean ages of onset for breast and pubic hair growth and for menses by race and ethnicity as well as odds ratios of having attained pubertal milestones among the 3 racial/ethnic groups studied in the NHANES. Tables 1 and 2 compare these results with those of the PROS study[1] and the analyses of the NHANES data for average ages of onset of breast and pubic hair growth and menses by Sun et al[24] and Chumlea et al[25], respectively. Age at menarche was estimated by Wu et al by both the status quo method as well as an estimate based on the self-reported age using a failure time model, both under the assumption of a normal distribution of the event (Table 2). Their mean ages for menarche differ slightly from those of the Chumlea et al analysis (see below) of the NHANES data published in January 2003 because of different statistical methods. Wu et al concluded that black girls enter puberty earliest, followed by Hispanic and then white girls. Numerous studies, including the 1997 PROS study, have found earlier puberty among black girls. The Wu et al analysis provides the important additional information that racial and ethnic differences among the NHANES populations are independent of select social and economic factors.

In the same issue of *Pediatrics*, the article by Freedman et al[22] looked at the relation of age at menarche to race, time period, and anthropometric dimensions by using the Louisiana population followed in the Bogalusa Heart Study. Their assessment of secular trends in menarcheal age between 1973 and 1994 found that the mean menarcheal age decreased by 9.5 months for black girls and 2 months for white girls over the 20-year time period. As in other studies, they also found that black girls matured earlier than white girls.

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The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (PANDAS) Subgroup: Separating Fact From Fiction

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Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood

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Summary

Background In children, exacerbations of tics and obsessive symptoms may occur after infection with group A β-haemolytic streptococci. If post-streptococcal autoimmunity is the cause of the exacerbations, then children might respond to immunomodulatory treatments such as plasma exchange or intravenous immunoglobulin (IVIG). We studied whether plasma exchange or IVIG would be better than placebo (sham IVIG) in reducing severity of neuropsychiatric symptoms.

Methods Children with severe, infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders, including Tourette syndrome, were randomly assigned treatment with plasma exchange (five single-volume exchanges over 2 weeks), IVIG (1 g/kg daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG). Symptom severity was rated at baseline, and at 1 month and 12 months after treatment by use of standard assessment scales for OCD, tics, anxiety, depression, and global function.

Findings 30 children entered the study and 29 completed the trial. Ten received plasma exchange, nine IVIG, and ten placebo. At 1 month, the IVIG and plasma-exchange groups showed striking improvements in obsessive-compulsive symptoms (mean improvement on children's Yale-Brown obsessive compulsive scale score of 12 [45%] and 13 [58%], respectively), anxiety (2·1 [31%] and 3·0 [47%] improvement on National Institute of Mental Health anxiety scale), and overall functioning (2·9 [33%] and 2·8 [35%] improvement on National Institute of Mental Health global scale). Tic symptoms were also significantly improved by plasma exchange (mean change on Tourette syndrome unified rating scale of 49%). Treatment gains were maintained at 1 year, with 14 (82%) of 17 children "much" or "very much" improved over baseline (seven of eight for plasma exchange, seven of nine for IVIG).

Interpretation Plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders. Further studies are needed to determine the active mechanism of these interventions, and to determine which children with OCD and tic disorders will benefit from immunomodulatory therapies.

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Introduction

Obsessive-compulsive disorder (OCD) and tic disorders are common in childhood, affecting 1–2% of school-aged children and adolescents. The obsessional thoughts and compulsive rituals of OCD are generally chronic and disabling, and cause serious psychological distress and lifelong impairment of social and occupational functioning.[1] Treatment with serotonin reuptake blocking drugs, behaviour therapy, or both, helps more than 75% of patients, but most show only a partial response, and relapse when medication is discontinued. Tic disorders, including Tourette syndrome, have a more variable course than OCD, since the severity of symptoms waxes and wanes. About two in three of these patients will have complete or partial remission of symptoms during adolescence.[2] Medications such as neuroleptics can reduce tic severity, but do not eliminate them.

The cause of OCD and tic disorders is unknown, although the two disorders may have a common cause that is a combination of genetic and environmental factors.[3] Post-streptococcal autoimmunity has been postulated as one possible environmental trigger, and Sydenham's chorea, the neurological manifestation of rheumatic fever, has been proposed as a potential model of pathophysiology.[4]

Molecular mimicry is thought to play a part in the aetiology of Sydenham's chorea, through a process in which antibodies against group A β-haemolytic streptococci crossreact with neuronal cells to produce inflammation in the central nervous system (particularly within the basal ganglia), resulting in chorea, muscle weakness, and emotional lability.[5,6] In some cases, obsessions, compulsions, and tics may also be mediated by post-streptococcal autoimmunity. Several studies have shown crossreactive antistreptococcal antibodies in children with OCD and tic disorders, and a marker of susceptibility to rheumatic fever has been shown in a subgroup of these patients.[7–9] The subgroup shares a unique clinical course and is identified by the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).[10]

The pathophysiology proposed for Sydenham's chorea suggests that treatments that interrupt the autoimmune process might lessen the severity of symptoms. Preliminary results for a controlled trial of plasma exchange and intravenous immunoglobulin (IVIG) in patients with Sydenham's chorea showed efficacy of both treatments.[11] We hypothesise that if the aetiology of PANDAS is similar to that in Sydenham's chorea, then immunomodulatory therapies might also be effective treatments for exacerbated neuropsychiatric symptoms.[12] Steroid therapy was not a viable treatment option for our study, because tics and OCD may worsen during steroid administration.[13] Plasma exchange and IVIG were chosen as the active treatments because of their record of safety and effectiveness in several childhood and adult immune-mediated diseases, as well as anecdotal reports of symptom improvement in patients with

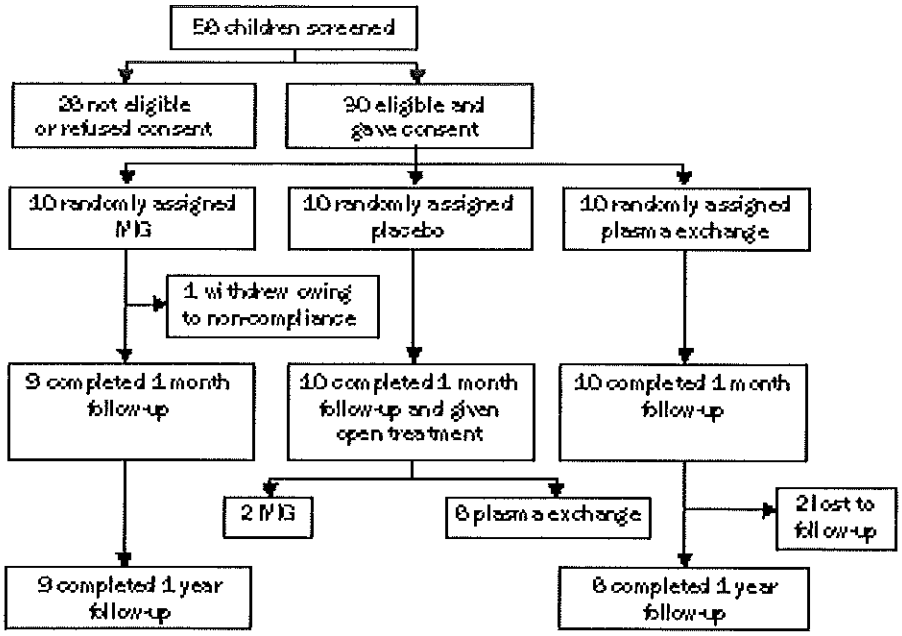

Figure 1: Trial profile

infection-triggered exacerbations of OCD.[12,14-16] We aimed to show whether plasma exchange and IVIG would be better than placebo in decreasing neuropsychiatric symptoms in children with infection-triggered exacerbations of OCD and tic disorders.

Patients and methods

Patients

Children aged 5–14 years were recruited nationwide over 4 years via letters to paediatricians, neurologists, and psychiatrists. Referrals were screened by telephone interview to assess study eligibility. Those parents who were interested in the treatment protocol and whose children fitted our criteria were assessed at the National Institute of Mental Health outpatient clinic. Eligibility criteria were: a tic disorder, obsessive compulsive disorder, or both, that met definitions in the Diagnostic and Statistical Manual of Mental Disorders;[17] onset of neuropsychiatric signs and symptoms before puberty; a history of sudden onset of signs and symptoms, or an episodic course characterised by abrupt exacerbations and periods of partial or complete remission; evidence of and association between streptococcal infection and onset or exacerbation of signs and symptoms (requirements for the PANDAS subgroup);[10] and current exacerbation severe enough to cause significant distress and interfere with the child's social functioning in at least two spheres (home, school, social relations).

Children were excluded from the study if they had a history of Sydenham's chorea or rheumatic fever, autism, schizophrenia or other psychotic disorder, a neurological disorder other than a tic disorder, an autoimmune disorder, or other medical illness. Immunoglobulin concentrations were measured and children were excluded from the study if they had IgA deficiency (a contraindication to IVIG administration).[18]

At initial assessment, most children were taking neuropsychotropic medications, including serotonin reuptake inhibitors for OCD symptoms, and clonidine or neuroleptic medications for tics. These medications were continued at constant dose for 1 month, after which time dose could be adjusted as needed by each child's physician. Oral penicillin or erythromycin was given during follow-up according to American Heart Association guidelines for prophylaxis against rheumatic fever, to protect against streptococcal infections.

The study protocol was approved by the institutional review board at the National Institute of Mental Health, Bethesda, MD, USA. Each parent and child gave consent or assent, respectively, for the investigation.

Study design

Children who met criteria for study entry underwent baseline medical, neurological, and psychiatric assessment. This assessment included a structured psychiatric interview,[19] echocardiography, and laboratory studies, including antistreptolysin-O test, antistreptococcal deoxyribonucleic B titres, and throat culture. We measured severity of neuropsychiatric signs and symptoms with the Tourette syndrome unified rating scale,[20-22] children's Yale-Brown obsessive compulsive scale,[23] global assessment scale,[24] clinical global impression scales of symptom severity and change,[25] and the National Institute of Mental Health rating scales for global functioning, anxiety, and depression.[26] The latter scales were used as a template for a new measure, the National Institute of Mental Health emotional lability scale, which we used to rate irritability and emotional lability on a scale from 0 (no irritability) to 4 (very irritable, oppositional behaviour daily). The global assessment scale is a global assessment of functioning in which high scores show better psychosocial functioning and low scores show greater impairment. On all the other rating scales, scores decrease as symptoms improve.

After baseline assessment, children were randomly assigned plasma exchange, IVIG, or placebo (saline solution) by randomisation chart. Investigators and study participants were unaware of whether the child received IVIG or placebo, but were aware of who received plasma exchange. Children randomly assigned IVIG or placebo received 1 g/kg IVIG (Gammagard, Hyland Division, Baxter Healthcare, Deerfield, IL, USA) or the same amount of saline solution daily for 2 consecutive days. To maintain double masking, the bottles and tubing were shielded from view, and all patients were treated with diphenhydramine and paracetamol (acetaminophen) to lessen the occurrence of side-effects (nausea, vomiting, headache), which might have revealed the active treatment.

Plasma exchange was done in the Department of Transfusion Medicine of the National Institute of Health Clinical Center. One plasma volume (45 mL/kg bodyweight) was exchanged in each procedure, and five or six procedures were done, once a day or on alternate days, to complete a course in 10–12 days. Exchanges were done by use of a Spectra apheresis device (Cobe, Lakewood, CO, USA) with citrate anticoagulant (acid citrate dextrose formula A, ratio 13:1). 80% of the replacement fluid was 5% albumin, and the remainder was normal saline. External jugular venous access with a double-lumen central venous catheter was used in seven children; in the other three children, bilateral antecubital veins were used. Symptoms shown during apheresis were recorded as mild, moderate, or severe adverse effects depending on degree of discomfort and ability to continue with the procedure.

Medication	Plasma exchange (n=10)	IVIG (n=9)	Placebo (n=10)
None	3	4	4
Serotonin reuptake inhibitor	2	3	2
Serotonin reuptake inhibitor plus antidepressant	0	1	3
Neuroleptic	2	0	1
Neuroleptic plus serotonin uptake inhibitor	3	1	0

Table 1: **Medication use at baseline in each study group**

Treatment outcome was assessed at 1 month and 1 year after start of therapy. Because of differences in treatment duration (2 days for IVIG, 10–12 days for plasma exchange), the first follow-up assessment was 2–4 weeks after cessation of therapy. This assessment consisted of a standardised neurological examination and the same ratings of symptom severity were used to assess baseline status. After symptom ratings at 1 month were completed, the IVIG/placebo masking was broken. If the child had received placebo and had no improvement in symptoms, open treatment with IVIG or plasmapheresis was offered according to protocol requirements—thus, 1-year follow-up ratings are not available for the placebo group.

Statistical analysis

To measure differences between groups at baseline and after treatment, we used repeated-measures ANOVA on each of the symptom-severity ratings by use of the SAS statistical programme (version 5). We used Duncan post-hoc analysis to analyse significant findings ($p \leq 0.05$ throughout). Differences in baseline severity and degree of symptom change were assessed by ANOVA, χ^2 test of homogeneity, or paired t test, as appropriate. We used Pearson product-moment correlations to assess relations between baseline variables and outcome measures. Results are presented as mean (SD).

Results

Baseline characteristics

We screened more than 200 children by telephone; 58 underwent face-to-face screening in our clinic. 28 children did not meet eligibility criteria or were unwilling to participate in the randomised trial. 30 children (19 boys, 11 girls) were enrolled in the study (figure 1). One girl (IVIG group) left the study in the first week because of non-compliance; the other 29 completed the ratings at 1 month (ten plasma exchange, ten placebo, nine IVIG). Two children in the plasma-exchange group were lost to follow-up (at 4 and 6 months, respectively) before the assessment at 1 year.

At baseline, the three study groups were similar in age, primary diagnosis, duration of exacerbation, use of psychotropic medications, and presence of antistreptococcal titres. There were no differences in mean age at study entry (plasma exchange 10·3 years [SD 2·8]; IVIG 9·1 [2·4]; placebo 9·4 [2·3], p=0·8), or in the mean duration of acute illness or exacerbation before study entry (plasma exchange 29·1 weeks [49·4]; IVIG 12·3 [6·4]; placebo 10·5 [4·0], p=0·3). Medication use was similar in each group (table 1). The number of children who had started or increased medication dosage less than 2 months before study entry was also similar among the three groups (p=0·8). Treatment groups had similar numbers of children with a primary diagnosis of tic disorder (IVIG, two; placebo, three; plasma exchange, five) or OCD (IVIG, seven; placebo, seven; plasma exchange, five; p=0·3). The plasma exchange and placebo groups each had six children with OCD and tics, two with OCD alone, and two with tics alone. The IVIG group had four children with OCD and tics, and five with OCD alone. At baseline, symptom severity was similar among the three groups for all measures (table 2), except tic severity, which was greatest in the plasma-exchange group (p=0·02).

Throat cultures were negative at baseline in all subjects. Titres of antistreptolysin-O were similar among the three groups (plasma exchange: three negative, seven positive, mean 458 [SD 229]; IVIG: five, four, mean 517 [290]; placebo: five, five, mean 350 [147]). Antistreptococcal deoxyribonucleic B titres were also similar among the three groups (plasma exchange: five negative, five positive, mean 452 [SD 278]; IVIG: two, seven, mean 780 [434]; placebo: three, seven, mean 546 [391]). There was no correlation between baseline titres and degree of treatment response for any group, or for the study population as a whole.

Response to treatment

Of the ten children randomly assigned plasma exchange, all succesfully completed the planned course of five (n=6) or six (n=4) procedures. Children's weight ranged from 22 kg to 61 kg (mean 38·9 kg). The mean plasma volume exchanged per procedure was 1667 mL [SD 552]. Whole blood flow rates ranged from 24–56 mL/min, depending on the child's weight and citrate tolerance. Time to completion of the procedures ranged from 85 min to 121 min (mean 101 min [11]). A 10% decrease in packed-cell volume was observed during the course of the exchanges; the platelet count did not change.

Adverse reactions (pallor, dizziness, nausea) occurred in seven patients, two of whom also had vomiting. Significant bradycardia or hypotension did not occur, and no patients had paraesthesia or muscle cramping. Three children also complained of feeling anxious and were restless during the procedures, but none required medication. Reactions were most common during the first procedure, and tended not to recur during subsequent exchanges. Treatment consisted of postural manipulation and temporary cessation of the

Rating scores for symptom severity	IVIG (n=9)			Placebo (n=10)			Plasma exchange (n=10)			p for difference between placebo and active treatment
	Baseline	1 month	% change	Baseline	1 month	% change	Baseline	1 month	% change	
Obsessions and compulsions	26·7 (5·9)	14·7 (10·8)	45*	23·0 (13·6)	22·1 (13·1)	3	22·5 (13·4)	9·5 (10·1)	58*	0·006
Tics	6·8 (9·2)	5·5 (7·7)	19	11·0 (9·5)	9·7 (9·1)	12	21·7 (14·7)	11·0 (9·2)	49*	0·005
Sum of obsessions, compulsions, and tics	33·4 (10·2)	20·2 (14·3)	40*	34·0 (7·3)	31·8 (8·9)	6	44·2 (15·2)	20·5 (12·0)	54*	0·001
Global impairment	8·7 (1·0)	5·8 (1·9)	33*	7·7 (1·6)	7·7 (1·6)	0	8·0 (2·7)	5·2 (2·3)	35*	0·0009
Psychosocial functioning	56·0 (9·7)	67·4 (12·1)	20	58·3 (10·5)	59·9 (11·4)	3	56·0 (13·1)	73·0 (15·3)	30	0·2
Anxiety	6·8 (1·2)	4·7 (1·6)	31*	6·2 (2·4)	6·0 (2·3)	3	6·4 (2·8)	3·4 (1·8)	47*	0·001
Depression	5·4 (2·1)	4·0 (2·1)	26*	6·2 (2·5)	6·3 (3·0)	2	5·2 (2·2)	2·9 (1·7)	44*	0·002
Global severity	4·7 (0·8)	3·4 (1·2)	26*	4·8 (0·4)	4·8 (0·5)	1	5·0 (0·9)	3·2 (1·0)	36*	0·0001
Emotional lability	6·2 (2·2)	4·4 (2·4)	29*	6·5 (2·6)	6·6 (2·6)	2	6·3 (2·1)	4·1 (1·8)	35*	0·001

Data are mean (SD) or %. *% changed from baseline to 1 month follow-up in which paired t tests were significant at p<0·05.

Table 2: **Symptom severity at baseline and 1 month after treatment**

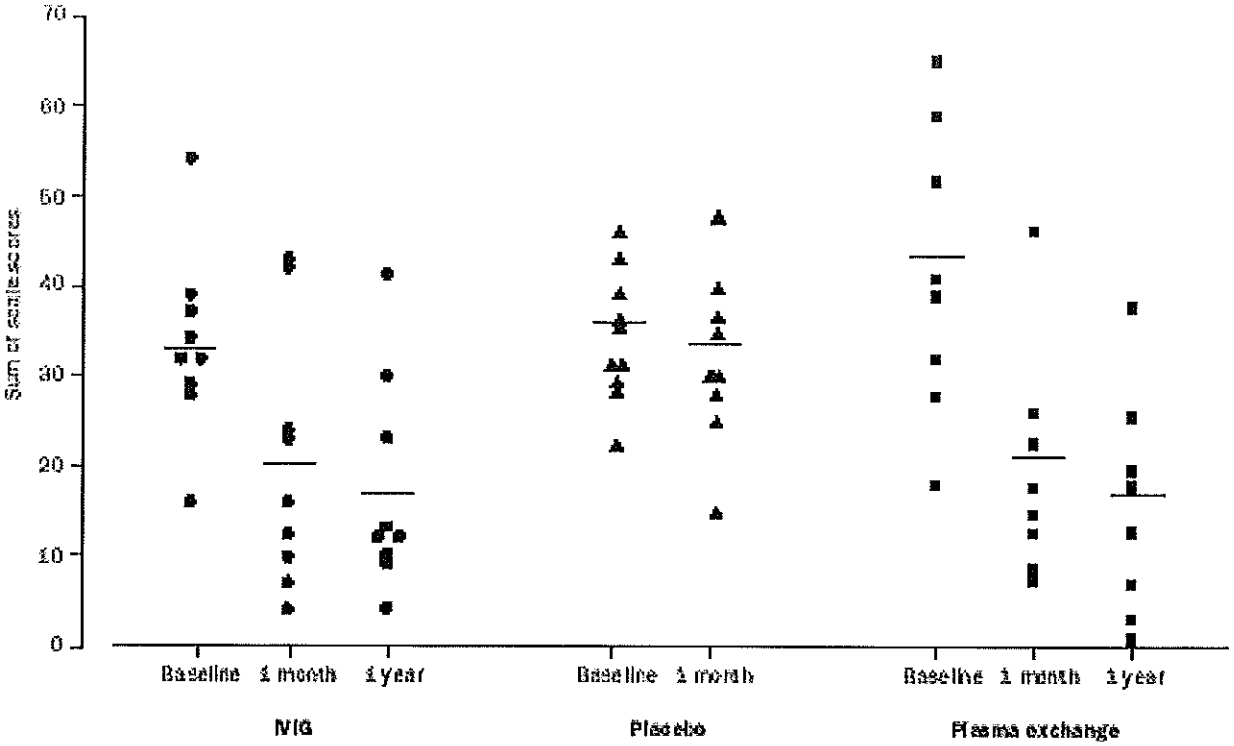

Figure 2: **Change in obsessive-compulsive disorder and tic severity at 1 month (all three groups) and 1 year (plasma exchange, IVIG)**
Scores are sum of Yale-Brown scores and Tourette syndrome unified rating scale scores. Horizontal bars are means.

procedure; no procedure had to be stopped prematurely due to an adverse event. There was no correlation between the occurrence of vasovagal, citrate, or hyperanxiety reactions and the type of venous access used (central *vs* peripheral).

In the IVIG group, the range of children's weight was 18·0 kg to 42·8 kg, and the range of infusion was 18–43 g/day (360–860 mL). Six children had adverse effects of mild to moderate severity, including nausea and vomiting (five), mild to moderately severe headache (three), and low-grade fever (four). These symptoms tended to occur during the second day of the infusion, and were relieved by hydration and additional doses of paracetamol and diphenhydramine. None was of sufficient severity to preclude completion of the IVIG infusion.

In the placebo group, the children's weight ranged from 16·9 kg to 49·5 kg, and the infusions ranged from 340 mL to 1 L. Two children experienced mild adverse effects of the infusion: both had stomachache (without nausea or vomiting), and one had mild headache. The symptoms were treated with paracetamol or diphenhydramine and did not interfere with completion of the placebo infusion.

1 month followup

At 1 month after treatment, the plasma exchange and IVIG groups showed striking improvements in obsessive-compulsive symptoms, anxiety, depression, emotional lability, and global functioning (table 2). Ratings done 1 month after treatment showed significant differences ($p \leq 0.05$) from baseline in the plasma exchange and IVIG groups for the children's Yale-Brown scale, the National Institute of Mental Health scales of anxiety, depression, emotional lability, and global function, and the clinical global impression severity scale. The plasma exchange group showed significant improvements in tic severity over placebo but the IVIG group did not, perhaps because baseline ratings were highest in the plasma exchange group. No group had significant improvements in global assessment scale (table 2).

At 1 month, global change scores for children in the plasma exchange and IVIG groups were improved by 48% and 41%, respectively (clinical global impression change 1·9 [SD 1·1] for plasma exchange and 2·4 [1·1] for IVIG). By contrast, placebo produced no change in overall symptom severity (change 4·1 [0·6]) or in specific symptom severity (table 2).

In the plasma-exchange group, symptom improvement usually occurred near the end of the first week of treatment, whereas in the IVIG group improvement was not usually seen until at least the third week after treatment. The plasma-exchange group appeared to have greater symptom relief than did the IVIG group (figure 2), with particularly

Rating score for symptom severity	IVIG (n=9)				Plasma exchange (n=8)				p for difference between groups
	Baseline	1 month	1 year	% change from baseline	Baseline	1 month	1 year	% change from baseline	
Obsession and compulsions	26·7 (5·9)	14·7 (10·8)	11·3 (5·5)	58*	22·9 (14·9)	9·5 (10·1)	6·9 (7·9)	70*	0·88
Tics	6·8 (9·2)	5·5 (7·7)	5·8 (8·7)	15	18·9 (14·0)	11·0 (9·2)	8·9 (9·6)	53*	0·06
Sum of obsessions, compulsions, and tics	33·4 (10·2)	20·2 (14·3)	17·1 (11·9)	49*	41·8 (16·0)	19·8 (12·3)	15·8 (12·5)	62*	0·29
Psychosocial functioning	56·0 (9·7)	67·4 (12·1)	70·6 (7·3)	26*	56·3 (14·6)	73·0 (15·3)	82·5 (12·9)	47*	0·28
Global severity	4·7 (0·8)	3·4 (1·2)	3·4 (0·7)	26*	5·0 (1·1)	3·2 (1·0)	2·8 (1·4)	45*	0·26

Data are mean (SD) or %. *% changes from baseline to 1 year in which paired *t* tests were significant at $p<0.05$.

Table 3: **Symptom severity at baseline and 1 year after treatment**

striking individual improvements in obsessive-compulsive symptoms (table 2).

The lack of placebo response was not the result of treatment resistance, since the children in the sham IVIG group showed improvement after open treatment with IVIG (two children) or plasma exchange (eight children). 1 month after active treatment, the mean clinical global impression change score for the ten children in the group was 2·6 (SD 1·3), with most children reported to be "very much improved". Obsessive-compulsive symptoms had decreased by 40% on average (mean Yale-Brown score decreased from 22 to 13·3) and tics by 17·5% (mean Tourette syndrome unified rating scale improved from 9·7 to 8·0). Overall functioning had also improved, as measured by the global assessment scale (14% increase from 60 to 68) and the clinical global impression scale (decreased from 4·8 to 3·7). Only two children failed to respond to active treatment (one given IVIG, one given plasma exchange). Both had tics without OCD, but this pattern was not associated with a lack of response among children in the plasma exchange and IVIG groups.

1 year follow-up

At 1 year after treatment, 17 children initially assigned active treatment were reassessed (plasma exchange, eight; IVIG, nine). Three children had had a second course of immunomodulatory therapy in the intervening months. One child in the plasma-exchange group was retreated with plasma exchange for a symptom exacerbation 10 weeks after initial treatment, one was treated with IVIG at 4 months, and one in the IVIG group had a second IVIG treatment at 2 months. At the time of their symptom exacerbations, all three children had a history of streptococcal exposure and increased antistreptococcal titres despite prescription of oral penicillin prophylaxis.

At baseline, 13 children (plasma exchange, six; IVIG, seven) used psychotropic medications for symptom relief. At 1 year's follow-up, six of these children (plasma exchange, two; IVIG, four) were taking an equivalent or higher dosage of medication, but seven (plasma exchange, four; IVIG, three) were on a lower dosage. Two of the 13 children had been able to discontinue medication because of symptom remissions.

Symptoms remained improved from baseline on all measures at the 1-year follow-up assessment. The most clinically meaningful improvements occurred in obsessive-compulsive symptoms, tic severity, and global measures of symptom severity and psychosocial functioning (table 3). Our clinical impression after 1 year's follow-up was that plasma exchange was better than IVIG, particularly for treatment of symptoms of OCD. The symptom rating confirmed these impressions (table 3, figure 2).

The change in global assessment scale scores from baseline to 1 year follow-up (table 2) shows a striking improvement in psychosocial function. In general children who previously had "symptom impairments in several social areas" now had "good functioning in all areas". These improvements were also shown by the clinical global impression change score: the IVIG group was rated as "much improved" (score 2·3 [SD 1·1], 53%) and the plasma-exchange group was "very much improved" (1·75 [0·9], 70%). 14 (82%) children had symptom reductions of at least 50%. Parents commonly reported that "my child's back to his old self again" and children reported that "things are a lot easier now".

Discussion

Plasma exchange and IVIG were both better than placebo in the treatment of exacerbations of neuropsychiatric symptoms in children with OCD and tic disorders. Both active treatments gave rapid and sustained improvements in global functioning, depression, emotional lability, and obsessive-compulsive symptoms, whereas placebo had little or no effect. The lack of a placebo effect is not surprising, given the number of studies in which placebo has failed to relieve obsessive-compulsive symptoms.[27] However, the lack of placebo response is still of note in our trial because the invasive nature of therapies might have led to a robust placebo effect. The adverse effects of IVIG treatment could have served to break the blinding in the IVIG and placebo groups. All children were aware of the potential for nausea, vomiting, and headache in association with IVIG treatment, and children who did not have these side-effects may have concluded that they had received placebo. The data did not reveal such a pattern—there was no relation between degree of adverse effects and symptom improvement in either the IVIG group or the placebo group. Without evidence of efficacy, the potential risks of sham apheresis were not justifiable in paediatric research, so some of the benefits seen in the plasma-exchange group might have been due to the placebo effect of a presumed high-technology intervention. If that were the case, however, the benefits should have waned over time, but they did not, and the plasma-exchange group continued to show striking improvements 1 year after the apheresis procedures.

Acute adverse effects of plasma exchange were frequent, but mild. Although most patients had dizziness or nausea, none developed paraesthesias, muscle spasm, hypotension, or bradycardia. We could not easily determine whether these symptoms were vagal in origin or due to citrate-induced hypocalcaemia. In all cases, symptoms resolved rapidly with postural manipulation and transient interruption of the apheresis procedure. Overall, the safety profile of apheresis in these children was excellent. The children appeared to tolerate plasma exchange better than IVIG, since the side-effects of IVIG (nausea, vomiting, headache) persisted for 12–24 h whereas those related to apheresis were brief and limited to the procedure period.

More than 80% of the patients who received IVIG or plasma exchange remained "much" or "very much" improved at 1 year, and their symptoms were in the subclinical range of severity. These results are particularly striking when compared with previous reports of the intractable nature of paediatric OCD and tic disorders; long-term outcome studies in OCD have shown that less than one third of patients had clinically meaningful symptom improvements.[28]

It is intriguing that a single course of IVIG or plasma exchange gave such sustained treatment effects. The original hypothesis of our study was that both IVIG and plasma exchange would reduce symptom severity by blocking (IVIG) or removing (plasma exchange) the antistreptococcal antibodies that were cross-reacting with neuronal tissue.[4-6] A single treatment course would therefore give lasting benefits if streptococcal infections were prevented by antibiotic prophylaxis. The hypothesis suggests that the rate of improvement with plasma-exchange treatment should be directly proportional to the rate of antibody removal. This improvement occurred in a few instances, with symptoms beginning to improve at about the time of the third exchange, and additional benefits shown after the fourth and fifth treatments.

However, most of the children did not have such a direct response, and showed the greatest improvement in the days and weeks following cessation of the apheresis procedure. This pattern could also be predicted by the hypothesis, since the inflammatory changes caused by the autoantibodies would take some time to resolve. The model is unable to explain why symptom recrudescences occurred so rapidly after streptococcal infections (since titre rises appear to occur more slowly), or to explain the mechanism by which peripheral effects of IVIG and plasma exchange could be translated across the blood-brain barrier to give volumetric changes in basal ganglia structures.[30] The actions of IVIG and plasma exchange are too broad to be helpful in delineating the nature of the improvements or in determining the pathophysiology of the neurospychiatric symptoms. Trials with more selective and specific immunomodulatory agents may answer the questions raised by our study, and may give information about the types of patients who will respond to immunomodulatory therapy.

Our results suggest that plasma exchange and IVIG are highly beneficial to a subgroup of patients with tics and obsessive-compulsive symptoms, but the study does not support the routine use of immunomodulatory agents in OCD and tic disorders. The children who we studied are not likely to be representative of typical paediatric patients with OCD or tic disorders, since they were selected from a much larger group of children on the basis of a history consistent with PANDAS.[10] Given the specificity of the entry criteria, the results cannot be extrapolated to all patients with OCD and tics. Because the mechanism of action of the therapeutic response is unknown, the additional groups of patients that might benefit from treatment with IVIG or plasma exchange is not clear. To assess this issue, the eligibility criteria have been modified to allow study of a broader cross-section of patients with OCD and tic disorders. These trials will attempt to assess whether IVIG and plasma exchange are effective in treating symptom exacerbations that are not triggered by streptococcal infections, and whether the treatments can benefit patients with chronic symptoms.

Contributors

Susan Perlmutter was responsible for patient care during the second and third years of the study, participated in data analysis and interpretation, and prepared the first draft of the paper. Susan Leitman was co-principal investigator of the study, and contributed to data acquisition, analysis, and interpretation, and to preparation of the paper. Marjorie Garvey was medically responsible for the first year of the study, and contributed to data acquisition and interpretation. Susan Hamburger and Elad Feldman had primary responsibility for data analysis and presentation. Henrietta Leonard was co-principal investigator of the study, involved in study design, and data interpretation. Susan Swedo was the principal investigator for the study, responsible for study design and direction of data acquisition, analysis, and interpretation. She prepared the final paper and reviston.

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References

1 March JS, Leonard HL, Swedo SE. Obsessive-compulsive disorder. In: March JS, ed. Anxiety disorders in children and adolescents. New York: Guilford Press, 1995: 251–75.

2 Leckman JF, Peterson BS, Pauls DL, Cohen DJ. Tic disorders. *Psychiatric Clin North Am* 1997; **20**: 839–61.

3 Walkup JT, LaBuda MC, Singer HS, Brown J, Riddle MA, Hurko O. Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. *Am J Hum Genet* 1996; **59**: 684–93.

4 Swedo SE. Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. *JAMA* 1994; **272**: 1788–91.

5 Zabriskie JB. Rheumatic fever: the interplay between host, genetics, and microbe. *Circulation* 1995; **71**: 1077–86.

6 Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RC. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *J Exp Med* 1976; **144**: 1094–110.

7 Kiessling LS, Marcotte AC, Culpepper L. Antineuronal antibodies in movement disorders. *Pediatrics* 1993; **92**: 39–43.

8 Singer HS, Giuliano JD, Hansen BH, et al. Antibodies against human putamen in children with Tourette syndrome. *Neurology* 1998; **50**: 1618–24.

9 Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. *Am J Psychiatry* 1997; **154**: 110–12.

10 Swedo SE, Leonard HL, Mittleman BB, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): a clinical description of the first fifty cases. *Am J Psychiatry* 1997; **155**: 264–71.

11 Garvey MA, Swedo SW, Shapiro MB, et al. Intravenous immunoglobulin and plasmapheresis as effective treatments of Sydenham's chorea. *Neurology* 1996; **46**: A147.

12 Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 1995; **34**: 307–11.

13 Jonasson G, Wilkinson SR. Prednisolone-induced obsessive-compulsive behaviour in a child. *Tidsskr Nor Laegeforen* 1993; **113**: 3162–66.

14 Barron KS, Sher MR, Silverman ED. Intraveous immunoglobulin therapy: magic or black magic. *J Rheumatol* 1992; **19**: 94–97.

15 The Guillain-Barre Syndrome Study Group. Plasmapheresis and acute Guillain-Barre syndrome. *Neurology* 1985; **35**: 1096–104.

16 Tucker DM, Leckman JF, Scahill L, et al. A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 1684–91.

17 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn. Washington, DC: American Psychiatric Association, 1987.

18 Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. *Drug Saf* 1993; **9**: 254–62.

19 Welner Z, Reich W, Herjanic B, Jung KG, Amado H. Reliability, validity, and parent-child agreement studies of the diagnostic interview for children and adolescents (DICA). *J Am Acad Child Adolesc Psychiatry* 1987; **26**: 649–53.

20 Kurlan R, Riddle M, Como P. Tourette syndrome unified rating scale. New York: Tourette Syndrome Association, 1988.

21 Kurlan R, McDermott MP. Rating tic severity. In: Kurlan R, ed. Handbook of Tourette's syndrome and related tic and behavioural disorders. New York: Marcel Dekker, 1993: 199–220.

22 Leckman JF, Towbin KE, Ort SI. Clinical assessment of tic disorder severity. In: Cohen DJ, Bruun R, Leckman JF, eds. Tourette's syndrome and tic disorders: clinical understanding and treatment. New York: Wiley & Sons, 1988: 55–78.

23 Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale-Brown obsessive compulsive scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 844–52.

24 Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983; **40**: 1228–31.

25 Guy W (ed). ECDEU assessment manual for psychopharmacology: US Department of Health, Education, and Welfare, 1976: 217–22.

26 Murphy DL, Pickar D, Alterman IS. Methods for quantitative assessment of depressive and manic disorders. In: Burdock EI, Sudilovsky A, Gershon S, eds. The behaviour of psychiatric patients. New York: Marcel Dekker, 1982; 355–92.

27 DeVeaugh-Geiss J, Moroz G, Biederman J, et al. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder—a multicentre trial. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 45–49.

28 Leonard HL, Swedo SE, Lenane MC, et al. A 2-to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. *Arch Gen Psychiatry* 1993; **50**: 429–39.

29 Giedd JN, Rapoport JL, Leonard HL, Richter D, Swedo SE. Case study: acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 913–15.